In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: September 29, 2023

ZACHARIA FARAG,	*	No. 17-714V
Petitioner,	*	Special Master Sanders
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Mark T. Sadaka, Law Offices of Sadaka Associates, LLC, Englewood, NJ, for Petitioner.
Dorian Hurley, United States Department of Justice, Washington, DC, for Respondent.

DECISION ON ENTITLEMENT[1]

On May 31, 2017, Lynn Farag filed a petition for compensation in the National Vaccine Injury Compensation Program ("the Program")[2] on behalf of her then-minor son Zacharia Farag ("Petitioner"). Pet., ECF No. 1. Ms. Farag alleged that the human papillomavirus ("HPV") vaccine Petitioner received on May 16, 2016, caused him to suffer from alopecia areata ("AA")[3] totalis.[4] *See generally id.*

[1] Because this Decision contains a reasoned explanation for the action taken in this case, it must be made publicly accessible and will be posted on the United States Court of Federal Claims' website, and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the Decision will be available to anyone with access to the internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will redact such material from public access.

[2] National Childhood Vaccine Injury Act of 1986, Pub L. No. 99-660, 100 Stat. 3755 ("the Vaccine Act" or "Act"). Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

[3] Alopecia areata is "patchy, nonscarring, asymmetric hair loss, sometimes reversible, occurring in sharply defined areas of the scalp or beard." *Dorland's Illustrated Medical Dictionary* 53 (33rd ed. 2020) [hereinafter "*Dorland's*"].

[4] Total alopecia, or alopecia totalis, is "complete loss of hair from the entire scalp, resulting from progression of alopecia areata." *Dorland's* at 53.

After carefully analyzing and weighing all the evidence and testimony presented in this case in accordance with the applicable legal standards,[5] I find that Petitioner has failed to provide preponderant evidence that the HPV vaccine he received on May 16, 2016, caused him to develop alopecia. Accordingly, Petitioner is not entitled to compensation.

I. Procedural History

Ms. Farag filed a petition on behalf of Petitioner on May 31, 2017. Pet. Ms. Farag filed medical records on June 6, 2017, as well as additional medical records and a statement of completion on July 11, 2017. Pet'r's Exs. 1–2, ECF No. 6; Pet'r's Exs. 3–4, ECF No. 8; ECF No. 9.

On September 19, 2017, Respondent filed his Rule 4(c) report recommending that compensation be denied. Resp't's Report, ECF No. 11. Following a Rule 5 conference held on October 17, 2017, I directed Ms. Farag to file an expert report. Order at 1, ECF No. 12. On October 18, 2017, Ms. Farag filed photographs documenting Petitioner's injury. Pet'r's Ex. 5, ECF No. 13-1. She then filed her affidavit on November 9, 2017. Pet'r's Ex. 6, ECF No. 14-1.

On November 21, 2017, Ms. Farag filed an expert report from M. Eric Gershwin, M.D. Pet'r's Ex. 7, ECF No. 15-1. Ms. Farag submitted medical literature on December 6, 2017. Pet'r's Exs. 8–17, ECF No. 17; Pet'r's Exs. 18–27, ECF No. 18; Pet'r's Exs. 28–37, ECF No. 19; Pet'r's Exs. 38–47, ECF No. 20. Pet'r's Exs. 48–57, ECF No. 21; Pet'r's Exs. 58–67, ECF No. 22; Pet'r's Exs. 68–77, ECF No. 23; Pet'r's Exs. 78–80, ECF No. 24. Respondent filed an expert report from Mehrdad Matloubian, M.D., Ph.D., as well as his curriculum vitae ("CV") and accompanying medical literature, on February 23, 2018. Resp't's Exs. A, A, Tabs 1–9, ECF No. 29; Resp't's Exs. A, Tabs 10–16, B, ECF No. 30. Ms. Farag filed a supplemental expert report from Dr. Gershwin and accompanying medical literature on March 22, 2018. Pet'r's Exs. 81–90, ECF No. 32. Respondent followed with a supplemental expert report from Dr. Matloubian on June 20, 2018. Resp't's Ex. C, ECF No. 35-1.

I held a status conference in this case on August 7, 2018, and the parties agreed that Ms. Farag would submit a settlement demand. Order at 1, ECF No. 38. After Ms. Farag submitted a settlement demand, Respondent filed a status report on December 21, 2018, stating that he was not interested in pursuing settlement. ECF No. 42. On December 24, 2018, Ms. Farag filed a status report requesting that this case be set for an entitlement hearing. ECF No. 43. Ms. Farag filed an additional medical record on February 22, 2021. Pet'r's Ex. 91, ECF No. 51-1. On June 28, 2021, I issued a decision awarding Petitioner's counsel interim attorneys' fees and costs. ECF No. 52.

On January 25, 2022, I set an entitlement hearing in this case for July 25–July 26, 2022. Hearing Order, ECF No. 56. Ms. Farag filed a prehearing brief on May 27, 2022. Pet'r's Prehearing Br., ECF No. 58. She filed Dr. Gershwin's CV on June 13, 2022. Pet'r's Ex. 92, ECF No. 60-1.

[5] While I have reviewed all of the information filed in this case, only those filings and records that are most relevant to the decision will be discussed. *Moriarty v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision.") (citation omitted); *see also Paterek v. Sec'y of Health & Hum. Servs.*, 527 F. App'x 875, 884 (Fed. Cir. 2013) ("Finding certain information not relevant does not lead to—and likely undermines—the conclusion that it was not considered.").

Respondent submitted his prehearing brief on June 27, 2022. Resp't's Prehearing Br., ECF No. 61. On June 28, 2022, I directed the clerk of court to amend the caption in this case because Petitioner reached the age of majority. Order at 1, ECF No. 62. Respondent filed Dr. Matloubian's updated CV and medical literature on July 18, 2022. Resp't's Exs. D–E, ECF No. 64. Petitioner filed additional medical literature and updated photos of his injury on July 18, 2022. Pet'r's Exs. 93–99, ECF No. 70; Pet'r's Ex. 100, ECF No. 71-1. Petitioner filed an affidavit on July 21, 2022, and an additional piece of medical literature on July 22, 2022. Pet'r's Ex. 101, ECF No. 74-1; Pet'r's Ex. 102, ECF No. 75-1.

An entitlement hearing was held remotely on July 25, 2022. Min. Entry, docketed July 25, 2022. Petitioner filed additional medical literature and a post-hearing brief on October 18, 2022. Pet'r's Exs. 103–09, ECF No. 81; Pet'r's Post-hearing Br., ECF No. 82. Respondent filed a responsive brief and medical literature on December 5, 2022. Resp't's Post-hearing Br., ECF No. 83; Resp't's Exs. F–H, ECF No. 84. Petitioner filed a reply on January 4, 2023. Pet'r's Reply, ECF No. 85.

This matter is now ripe for consideration.

II. Factual Background

A. Medical Records

Petitioner was born on February 17, 2004, and his pre-vaccination medical history is significant for autism. Pet'r's Ex. 2 at 6, ECF No. 6-2. On September 25, 2013, Petitioner's pediatrician indicated that "vaccine reactions have been reviewed."[6] *Id.* On March 8, 2016, Petitioner was diagnosed with strep throat and prescribed antibiotics by a pediatrician. *Id.* at 21–22. He received the Gardasil vaccine at issue during a well-child visit with his pediatrician, Dr. Jean Makhlouf, on May 16, 2016. *Id.* at 2, 23–27.

On June 20, 2016, Petitioner returned to Dr. Makhlouf with "complaints of hair loss on hairline near [his] forehead." *Id.* at 28. Dr. Makhlouf's assessment was tinea barbae[7] and tinea capitis.[8] *Id.* at 29. She prescribed griseofulvin[9] but noted that Petitioner potentially had alopecia. *Id.* She advised Petitioner to return in seven to ten days for a dermatology referral if his condition did not improve. *Id.*

On June 24, 2016, Petitioner presented to Dr. Andrea Kassim, a dermatologist, after receiving a referral from Dr. Makhlouf. Pet'r's Ex. 1 at 20, ECF No. 6-1. Petitioner reported that he was not seeing improvement after four days of griseofulvin treatment. *Id.* Dr. Kassim assessed Petitioner with AA on his scalp and directed him to discontinue griseofulvin. *Id.* at 22. Dr. Kassim

[6] It is unclear whether this means that Petitioner experienced adverse reactions to previous vaccinations.
[7] Tinea is "any of various dermaphytoses," which are superficial fungal infections. *Dorland's* at 1899. Tinea barbae is "tinea of the bearded area of the face and neck, usually occurring in those in contact with farm animals." *Id.* at 1899–1900.
[8] Tinea capitis is "tinea of the scalp, or sometimes the eyebrows and eyelashes, caused by" fungi. *Dorland's* at 1900.
[9] Griseofulvin is an antibiotic and antifungal medication. *Dorland's* at 798.

noted that Petitioner's hair loss had been occurring for "[w]eeks" and that he had "circular areas of hair loss[.]" *Id.* at 21. She stated that Petitioner's alopecia was of moderate severity. *Id.*

On August 23, 2016, Petitioner returned to the dermatology office and saw a different provider, Dr. Marc Glashofer. *Id.* at 16. Petitioner stated that his hair loss began two weeks after his Gardasil vaccination and that he had "no significant life or medical stressors prior to onset of concerns." *Id.* Petitioner denied scaling, itching, or pain effecting the areas of hair loss. *Id.* He reported no personal or family history of autoimmune or thyroid disorders. *Id.* On exam, Petitioner had "circular areas of hair loss" on his scalp as well as sparse brows. *Id.* at 17. Dr. Glashofer noted that Petitioner was "starting to loss lids[sic][.]" *Id.* Dr. Glashofer prescribed clobetasol propionate[10] and directed Petitioner to apply it to his scalp. *Id.* at 18.

Petitioner followed up with Dr. Glashofer on September 28, 2016, and presented with "no regrowth on areas of loss[.]" *Id.* at 12. On exam, Petitioner had lost more than 50% of the hair on his scalp. *Id.* at 13. He also had milia[11] on his right cheek and eyelid. *Id.* Dr. Glashofer directed Petitioner to continue his medication, and he discussed the possibility of further treatment with sulfasalazine[12] and immunotherapy. *Id.* at 14.

On November 16, 2016, Petitioner returned to Dr. Glashofer and presented with "complete loss of scalp, brow, lashes, [and] body hair[.]" *Id.* at 8. Petitioner reported no improvement with his topical corticosteroid. *Id.* The assessment was AA totalis. *Id.* at 10. Dr. Glashofer noted that Petitioner's "condition [was] severe enough to warrant the use of a[n oral] medication[,]" and Dr. Glashofer opined that "topicals alone will not be effective." *Id.* Dr. Glashofer prescribed sulfasalazine. *Id.* Petitioner again followed up with Dr. Glashofer on December 28, 2016, for "complete hair loss[.]" *Id.* at 4. Petitioner was directed to continue his sulfasalazine and topical corticosteroid. *Id.* at 6. On January 10, 2017, blood testing revealed slightly low hemoglobin, hematocrit, MCV, MCH, and MCHC as well as slightly high RDW and serum glucose. *Id.* at 24–27.

On January 25, 2017, Petitioner followed up with Dr. Glashofer for his alopecia. *Id.* at 1. Ms. Farag reported that Petitioner discontinued his topical corticosteroids because he was experiencing increased anger. *Id.* at 3. Dr. Glashofer directed Petitioner to discontinue sulfasalazine due to his bloodwork results. *Id.* Petitioner returned to Dr. Glashofer on March 22, 2017. Pet'r's Ex. 3 at 1, ECF No. 8-1. Dr. Glashofer noted that Petitioner had "[s]evere" alopecia that had been ongoing for "years[.]" *Id.* Dr. Glashofer directed Petitioner to continue with his topical corticosteroid. *Id.* at 3. Dr. Glashofer discussed beginning topical immunotherapy with SADBE treatment. *Id.*

On April 11, 2017, Petitioner presented to Dr. Makhlouf and was assessed with influenza. Pet'r's Ex. 4 at 13–14, ECF No. 8-2. Dr. Makhlouf noted that Petitioner had had "alopecia

[10] Clobetasol propionate is "a very high potency synthetic corticosteroid[.]" *Dorland's* at 367.
[11] A milium is "a tiny epidermal cyst that is a round, smooth, firm, white to yellow papule just under the skin." *Dorland's* at 1150.
[12] Sulfasalazine is an antibacterial sulfonamide. *Dorland's* at 1771.

universalis[13] for the past year [and was] not responding to treatment with steroid[s].” *Id.* at 13. Petitioner followed up with Dr. Glashofer on June 25, 2017.[14] Pet’r’s Ex. 91 at 18–20. Ms. Farag indicated that Petitioner had not started SADBE yet due to insurance issues. *Id.* at 20.

On January 24, 2018, Petitioner returned to Dr. Glashofer. *Id.* at 14–17. On exam, Petitioner had “complete hair loss and [loss of] brow/lashes with [the] exception of a fe[w] new hairs on scalp[.]” *Id.* at 14. Dr. Glashofer noted that Petitioner had been suffering from alopecia for one and a half years and that his condition “began after [G]ardasil vaccination[.]” *Id.* Dr. Glashofer prescribed a “trial of [A]llegra[15] based on anecdotal reports from [J]apan of benefit.”[16] *Id.* at 16. Dr. Glashofer continued to discuss options with Petitioner for immunotherapy. *Id.*

Petitioner followed up with Dr. Glashofer on January 21, 2019. *Id.* at 11–13. Petitioner presented with “minimal regrowth> 90% loss[and] loss of brows[.]” *Id.* at 11. Ms. Farag elected to pursue diphenylcyclopropenone (“DPCP”) treatment. *Id.* at 12.

On February 4, 2019, Petitioner returned to Dr. Glashofer. *Id.* at 8–10. Dr. Glashofer applied DPCP to Petitioner’s scalp and noted that Petitioner declined Allegra. *Id.* at 9. On February 11, 2019, Dr. Glashofer increased Petitioner DPCP dosage from .01% to .1% because Petitioner was not seeing results. *Id.* at 6–7. On exam during a February 18, 2019 follow-up, Petitioner had more than 80% hair loss. *Id.* at 3–4. Dr. Glashofer decreased Petitioner’s DPCP strength to .05% due to concerns about whether Petitioner could tolerate the higher dosage. *Id.* at 4. Dr. Glashofer again reduced the DPCP strength on February 27, 2019, because Petitioner was experiencing irritation. *Id.* at 1–2.

B. Affidavits and Fact Testimony

In her affidavit filed on November 9, 2017, Ms. Farag stated that, six days before his Gardasil vaccination, Petitioner’s “hair was so long [that a] hair dresser put it in a small ponytail.” Pet’r’s Ex. 6 ¶ 6. Ms. Farag recounted Petitioner’s May 16, 2016 vaccination and recalled that a few weeks later, during Memorial Day weekend of 2016, Petitioner complained that his hair was falling out. *Id.* ¶¶ 7–8. Ms. Farag recalled that Petitioner showed her a clump of hair and that she “noticed that a part of his frontal hairline was receding upward on one side of his scalp.” *Id.* ¶ 8. Ms. Farag stated that Petitioner’s hairline continued receding, creating a bald spot, in June. *See id.* ¶¶ 9–10. She noted that Petitioner’s alopecia continued progressing and that he was “completely bald and [had] lost all eye brow and body hair[]” by September 7, 2016. *Id.* ¶ 13. Ms. Farag stated that the medications Petitioner had tried “only result[ed] in behavioral changes and anemia[]” and that Petitioner was no longer taking medication for his condition at that time. *Id.* ¶ 14.

[13] Alopecia universalis, or universal alopecia, is “loss of hair over the entire body, resulting from progression of alopecia areata.” *Dorland’s* at 53.

[14] Petitioner’s Exhibit 91 does not indicate the dates of appointments. The dates for this exhibit refer to the date Dr. Glashofer signed each note.

[15] Allegra, or fexofenadine hydrochloride, is an antihistamine used to treat allergic rhinitis and chronic idiopathic urticaria. *Dorland’s* at 688.

[16] It is unclear whether Petitioner ever tried this treatment.

In his affidavit filed on July 21, 2022, Petitioner recalled that he began noticing hair loss during Memorial Day weekend of 2016. Pet'r's Ex. 101 ¶ 6. He noted that his hair loss continued and that he had a bald spot by his sixth-grade dance on June 9, 2016. *Id.* ¶ 8. Petitioner recounted presenting to his pediatrician, who initially diagnosed him with ringworm, and then to a dermatologist, who diagnosed Petitioner with AA. *Id.* ¶¶ 9–12. Like Ms. Farag, Petitioner recounted continuing hair loss during the summer of 2016. *Id.* ¶¶ 14–15. Petitioner discussed the social and emotional difficulties his hair loss had caused. *See id.* ¶¶ 17–24.

During the entitlement hearing, Petitioner testified that he was missing hair "[a]ll over[]" his scalp as well as his eyebrows and eyelashes. Tr. 19:16–20:1. He also noted that he did not have body hair. Tr. 26:8. Petitioner explained that missing his eyelashes was painful because things like snow and sand easily got into his eyes. Tr. 20:4–13. Petitioner recalled beginning to experience hair loss "around June[]" of 2016. Tr. 20:20–24. He explained that one day when brushing his hair, "a clump of hair started to fall out." Tr. 20:24–25. Like in his affidavit, Petitioner recalled initially being diagnosed with ringworm before presenting to a dermatologist. Tr. 21:13–22:5. Petitioner noted that his alopecia diagnosis shocked and upset his family and that his friends thought he had cancer. Tr. 22:24–23:13. Petitioner described how his alopecia affected his confidence and the bullying he endured. Tr. 23:14–24:14. Petitioner stated that, at the time of the hearing, he still distanced himself from people and experienced some bullying. Tr. 24:15–25:4. Petitioner testified that he was not taking medication for his alopecia as of the hearing date. Tr. 25:15–17. Petitioner explained that he did not want to pursue treatment because he did not think it would be effective. Tr. 25:23–25. He explained that he previously "took all these other treatments and everything, and it just did[not] work, [and his hair] barely grew back[]" before "f[alling] off again." Tr. 26:1–3. Petitioner testified that he recently presented to a new dermatologist, who explained that there are new treatments for alopecia but that they can cause bad side effects. Tr. 26:24–27:2.

During my questioning, Petitioner indicated that none of his family members, including older people, suffer from hair loss. Tr. 29:18–30:7. Petitioner explained that following his hair loss, his scalp sometimes felt oily and sometimes felt dry. Tr. 30:15–21. Petitioner denied feeling any kind of symptom prior to losing a patch of hair. Tr. 30:24–31:5. He explained that he "would just wake up, and it would be out." Tr. 31:4–5. Petitioner stated that he would "[m]aybe [feel] a little sting when [hair] fell" because it would come out when he was brushing his hair, but he otherwise did not feel physically unwell. Tr. 31:11–14. Petitioner noted that the hair on his scalp sometimes fell out during brushing and sometimes on its own. Tr. 31:15–19. He also noted his eyebrows "just fell out on their own." Tr. 31:20–22. He stated that he did not feel any symptom on his face before his eyebrows fell out. Tr. 31:24–32:1.

III. Experts

A. Expert Review

1. Petitioner's Expert, M. Eric Gershwin, M.D.

Dr. Gershwin received his medical degree from Stanford University in 1971. Pet'r's Ex. 92 at 1. He completed his internship and residency at Tufts-New England Medical Center in Boston, Massachusetts before working as a clinical associate in immunology at the National

Institutes of Health in Bethesda, Maryland. *Id.* at 2. He joined the faculty of the University of California School of Medicine in Davis, California in 1975 as an assistant professor of rheumatology and allergy. *Id.* He has been a full professor since 1981, and he was the chief of the medical school's division of rheumatology/allergy and clinical immunology for thirty-eight years. *Id.*; Tr. 34:24–25. He is board certified by the American Board of Internal Medicine with a subspecialty in rheumatology and by the American Board of Allergy and Clinical Immunology. Pet'r's Ex. 92 at 2. Dr. Gershwin has received numerous honors, is a member of multiple professional societies, and has served as an editor of various journals. *Id.* at 3–8. He is an author or editor of seventy-two books or monographs as well as an author of more than 1000 additional publications. *Id.* at 9–135. Dr. Gershwin testified that his publications "overwhelmingly" involve topics of autoimmunity. Tr. 39:7–9. Discussing his clinical experience, Dr. Gershwin testified that he has treated "patients with very complicated immune diseases[]" for the past ten to fifteen years and that he treats patients in rheumatology and immunology. Tr. 34:20–35:2. Dr. Gershwin acknowledged that he is not a dermatologist and does not treat patients with AA, but he noted that many of his patients with rheumatic diseases experience hair loss. Tr. 35:3–6. He also noted that he has "published on alopecia[] and [ ] did some of the early transplant work on alopecia skin . . . ." Tr. 35:7–10. During the entitlement hearing, Dr. Gershwin was admitted as an expert in internal medicine, immunology, and rheumatology. Tr. 39:21–40:4.

2. Respondent's Expert, Mehrdad Matloubian, M.D., Ph.D.

Dr. Matloubian received his medical degree and Ph.D. in virology from the University of California, Los Angeles in 1996. Resp't's Ex. D at 1, ECF No. 64-1. He completed an internship, a residency, a rheumatology fellowship, and a post-doctoral fellowship at the University of California, San Francisco between 1996 and 2004. *Id.* at 1–2. He joined the faculty of the University of California, San Francisco medical school in 2001, and he became a full professor three years before the entitlement hearing. *Id.* at 2; Tr. 99:1–2. He is a member of various professional societies and a recipient of various awards, and he is an author of more than forty-five publications. Resp't's Ex. D at 2–3, 10–15. Dr. Matloubian is board certified in internal medicine and rheumatology. *Id.* at 2. He noted that his "areas of expertise include T[17] and B cell[18] responses, especially to viruses as well as factors that regulate lymphocyte circulation and trafficking." Resp't's Ex. A at 1, ECF No. 29-1. He "actively evaluates and treats patients with complex autoimmune diseases at a tertiary referral center[.]" *Id.* Dr. Matloubian testified that he treats patients in his own clinical practice and attends on an inpatient rheumatology consult service. Tr. 99:7–15. He noted that he is an adult rheumatologist and often treats rheumatoid arthritis, lupus, and various other disorders. Tr. 99:25–100:4. He further noted that he treats adults who had "pediatric onset rheumatologic disease[.]" Tr. 100:4–5. Although he does not primarily treat patients with alopecia, Dr. Matloubian stated that he has treated patients with autoimmune diseases who also have alopecia. Tr. 100:18–25. During the entitlement hearing, Dr. Matloubian was admitted as an expert in rheumatology and immunology. Tr. 103:18–24.

[17] T cells, or T lymphocytes, are "the cells primarily responsible for cell-mediated immunity[.]" *Dorland's* at 1071.

[18] B cells, or B lymphocytes are "bursa-dependent lymphocytes in birds and their counterparts in nonavian vertebrates including human beings, the cells primarily responsible for humoral immunity, the precursors of antibody-producing cells (plasma cells)." *Dorland's* at 1070.

B. Expert Reports and Testimony

1. Petitioner's Expert, Dr. Gershwin

In his first expert report, Dr. Gershwin explained that "[a]lopecia areata consists of one or more circular bald patches around the scalp[]" while "[a]lopecia totalis includes complete loss of hair on the scalp and is the most extreme form of [AA]." Pet'r's Ex. 7 at 1 (citing Pet'r's Ex. 8 at 2, ECF No. 17-1).[19] He noted that AA and alopecia totalis are "considered inflammatory and non-scarring[]" and that AA occurs in about 1.7% of people at some point during their lifetime. *Id.* He explained that "alopecia universalis is diagnosed with 100% loss of both scalp and body hair." *Id.* at 2. Dr. Gershwin stated that alopecia is a systemic disease that can affect the nails and eyes in addition to the hair follicles. *Id.* (citing Pet'r's Ex. 10, ECF No. 17-3).[20]

He wrote that "[t]he genetic basis of alopecia is strongly supported by its observed heritability in first degree relatives, twin studies[,] and genetic linkage analysis of alopecia families." *Id.* (citing Pet'r's Ex. 11 at 1–2, ECF No. 17-4).[21] He noted that 10% to 42% of alopecia patients have a first-degree relative who is also affected. *Id.* Citing a paper by Martinez-Mir et al.,[22] Dr. Gershwin asserted that "[a] genome wide search for linkage of [twenty] families with alopecia consisting of 102 affected and 118 unaffected individuals demonstrated the association of [human leukocyte antigens ("HLA")][23] with alopecia [ ]." *Id.* (citing Pet'r's Ex. 12, ECF No. 17-5). Dr. Gershwin explained that multiple HLA class II genes are associated with alopecia and that alopecia sometimes involves certain class I HLA alleles. *Id.* (citing Pet'r's Ex. 12 at 3). He continued that "[a]long with these HLA alleles that potentially contribute to the diagnosis of alopecia, certain regions of the human genome are associated with more severe disease." *Id.* (citing Pet'r's Ex. 12 at 6). He stated that certain alopecia-associated alleles "are more or less specific to various ethnic identities, and therefore genetic associations depend on the patient's particular geographic location and ethnic background [ ]." *Id.*

In addition to genetic factors, Dr. Gershwin noted that "[c]linical and experimental studies showed that environmental insults such as emotional/physical stressors, hormones[,] and infections contribute to autoimmunity [ ]." *Id.* He explained that stress hormones "are known to affect alopecia" and that stressors including "exposure to ultraviolet light, natural and chemical bodily offenses, physical injury, and emotional distress[]" have been linked to alopecia. *Id.*

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[19] Naseeha Islam et al., *The autoimmune basis of alopecia areata: A comprehensive Review*, 14 AUTOIMMUNITY REVIEWS 81 (2015).
[20] Shabnam Madani & Jerry Shapiro, *Alopecia areata update*, 42(4) J. AM ACAD DERMATOL 549 (2000).
[21] Lawrence Scerri & Joseph L. Pace, *Identical twins with identical alopecia areata*, 27(5) J. AM ACAD DERMATOL 766 (1992).
[22] Amalia Martinez-Mir et al., *Genomewide Scan for Linkage Reveals Evidence of Several Susceptibility Loci for Alopecia Areata*, 80 AM J. HUMAN GENETICS 316 (2007).
[23] HLA are "histocompatibility antigens governed by genes of the HLA complex (the human major histocompatibility complex), a region on the short arm of chromosome 6 containing several genetic loci, each having multiple alleles." *Dorland's* at 103.

Dr. Gershwin noted that cytomegalovirus ("CMV") has been associated with alopecia but that this association has been refuted. *Id.* at 3 (citing Pet'r's Exs. 32–33, ECF Nos. 19-5–19-6).[24] He explained that other viruses, such as "hepatitis B, hepatitis C, Epstein-Barr, and swine flu have also been suggested to trigger alopecia [ ]." *Id.* He continued that "[t]heories have also been put forward regarding seasonal associations, with evidence of increased disease relapses between the months of February and March." *Id.* He explained that "[t]his may also be a result of the high multitudes of viruses in early spring, supporting the hypothesis that alopecia may be an effect of certain viral infections." *Id.*

Explaining the evidence that alopecia is an autoimmune disease, Dr. Gershwin noted that patients with alopecia often have one or more other autoimmune disorders. *Id.* He explained that the effectiveness of immunosuppressive agents in treating alopecia indicates that it is autoimmune and that HLA "has been reported to play a major role in the etiology of autoimmunity [ ]." *Id.* He averred that "[a] confirmation of this specific hypothesis in alopecia lies in the increased expression of specific HLAs in alopecia patients such as HLA-DR, HLA-A, HLA-B, and HLA-C, which are rarely seen in healthy individuals [ ] as well as the identification of a number of genetic risk factors within various innate and adaptive immunity gene loci [ ]." *Id.* He stated that "[t]he most widely affected hypothesis for the effector mechanism of alopecia is the destruction of the [hair follicle], an immune privilege site." *Id.* He continued that while individuals without alopecia maintain immune privilege within the hair follicle "in multiple ways, such as omitting [major histocompatibility complex ("MHC")][25] class 1 in the proximal outer root sheath [,] patients identified with alopecia have a strong association with those same MHC class 1 alleles." *Id.* He explained that "[a]utoreactive cytotoxic T cells[26] target specific autoantigens, especially melanogenesis-associated peptides expressed by anagen [hair follicles] that produce melanin pigment [ ]." *Id.* Cytokines[27] as well as natural killer ("NK") cells[28] have also been implicated in the breakdown of immune privilege in alopecia. *Id.* at 3–4.

Dr. Gershwin also discussed the "C3H/HeJ mouse[, which] is a spontaneous mouse model of alopecia, which manifests the clinical pathological features of human alopecia, including infiltration of CD8 + NKG2D + T cells from around the epithelial layers of" hair follicles." *Id.* at 4. He cited a study by Sundberg et al.,[29] who wrote that "[a] disease closely resembling human [AA] was found in a large production colony of C3H/HeJ mice that had no evidence of thyroid

[24] Robert B. Skinner, Jr., et al., *Alopecia Areata and Prescence of Cytomegalovirus DNA*, 273(18) JAMA 1419 (1995); María J. García-Hernández et al., *No Evidence of Cytomegalovirus DNA in Alopecia Areata*, 110(2) J. INVEST DERMATOL 185 (1998).

[25] MHC are "the genes determining the major histocompatibility antigens, in all species a group of closely linked multiallelic genes located in a small region on one chromosome[.]" *Dorland's* at 391.

[26] Cytotoxic T cells are "differentiated T lymphocytes that can recognize and lyse target cells bearing specific antigens recognized by their antigen receptors." *Dorland's* at 1070. Cytotoxic T cells are a type of CD8 T cell, which is a T cell that "carr[ies] the CD8 antigen[.]" *Id.* at 311.

[27] Cytokine is "a generic term for nonantibody proteins released by one cell population (e.g., primed T lymphocytes) on contact with a specific antigen, which act as intercellular mediators, as in the generation of an immune response." *Dorland's* at 460.

[28] NK cells are "cells capable of mediating cytotoxic reactions without prior sensitization against the target." *Dorland's* at 316.

[29] John P. Sundberg et al., *Alopecia Areata in Aging C3H/HeJ Mice*, 102 J. INVEST DERMATOL 847 (1994).

dysfunction or an infectious etiology." Pet'r's Ex. 66 at 1, ECF No. 22-9. The authors noted that they obtained the mice from a laboratory where many of the mice colonies "are housed in strict quarantine to maintain their specific pathogen-free status[]" and where "[e]xtensive quarterly monitoring of all mouse rooms and representative mice is done to verify the microbiologic status of mice within rooms." *Id.* at 8. They also noted that "[r]outine bacterial and mycotic cultures were prepared from skin biopsies and plucked hair from C3H/HeJ mice with and without alopecia[, and n]o pathogens were isolated nor were any visualized in histologic selections of skin using special stains in the mice cultured or in others from the production of breeding colonies." *Id.* Sundberg et al. wrote that "the changes in this non-scarring alopecia were limited to anagen follicles that were surrounded by mononuclear cells[, and t]his infiltrate, composed primarily of cytotoxic ($CD8^+$) and helper ($CD4^+$) T cells,[30] was associated with follicular and hair shaft dystrophy." *Id.* at 1. The "infiltrate was markedly reduced by intralesional injection of triamcinolone acetonide with subsequent hair regrowth in the affected site." *Id.* The authors concluded that "[p]edigree tracing of [the affected] mice suggests that this non-scarring alopecia may be an inherited disease." *Id.*

Although Sundberg et al. did not find an infectious etiology, Dr. Gershwin testified that "just because they have[not] found an antigen or they have[not] found an infection in highly inbred mice does[not] mean there[is] not an infection which is present." Tr. 181:22–25. He concluded that "[t]here[is something in these mice that[is] causing them to develop[] . . . CD8 T cells." Tr. 182:2–3. He continued that "in every one of these papers we[have] cited, the pathogenic mechanism is felt to be [follicle-specific] CD8 T cells." Tr. 182:7–9. Dr. Gershwin was "unaware of a clinical situation where [there are] organelle-specific cytotoxic T cells in the absence of an antigen. And just because you have[not] found the antigen does[not] mean it[is] not there." Tr. 182:11–14. Dr. Gershwin noted that "at the end of the day, it[is] not the infection. It[is] the immune response which are CD8 cells." Tr. 183:9–10. Dr. Gershwin emphasized, "the absence of an antigen does[not] make any difference. What[is] critical is there[is] a CD8 T cell response." Tr. 184:1–3.

Dr. Gershwin asserted that "[t]he mechanism that leads to alopecia includes [ ] genetic susceptibility and the generation of cytotoxic CD8 T cells." Pet'r's Ex. 7 at 4. He noted that "[i]mportantly, the signals required to generate CD8 T cells beyond the initial exposure are not required for proliferation[,] and indeed there is likely to be early immunological programming of such cytotoxic T cell expansion[ ]." *Id.* He noted that there have been other mechanisms proposed for AA, but he opined that the T cell reaction he discussed is the most likely mechanism. Tr. 70:25–71:4.

When asked during the entitlement hearing what causes AA, Dr. Gershwin stated that "the current thesis is that it[is] autoimmune in nature, that the immune system attacks the hair follicle." Tr. 42:4–7. While he acknowledged that AA has a genetic basis, he stated that it is influenced by environmental factors, "as with every autoimmune disease[.]" Tr. 43:5–11. During cross-examination, Dr. Gershwin acknowledged that "there are probably multiple causes[]" of AA but that it is "likely to be autoimmune." Tr. 61:8–12. He acknowledged that emotional and physical stressors can trigger alopecia without the introduction of a foreign antigen, but he also noted that

[30] Helper T cells are "differentiated T lymphocytes whose cooperation (help) is required for the production of antibody against most (T-dependent) antigens." *Dorland's* at 313.

these cases "tend not to be lifelong[]" and "tend to be a little more patchy." Tr. 61:23–62:3. He acknowledged that acute infections are not an established cause of AA. Tr. 62:12–14.

Summarizing his medical theory in this case, Dr. Gershwin wrote that Petitioner "received a vaccine that produced cytotoxic T cells that were directed at his hair follicles and which cross react with an epitope[31] or region of the Gardasil vaccine." Pet'r's Ex. 7 at 5. He continued that "[t]he kinetics and the production of such cytotoxic T cells is consistent and biologically plausible with the literature on the production of such cytotoxic T cells." *Id.* He explained that the mechanism is similar to the mouse model and "is due to molecular mimicry." *Id.*

Discussing molecular mimicry generally, Dr. Gershwin explained that it is a viable theory in autoimmunity. Tr. 49:5–8. He explained that "homology extends beyond what[is] called primary sequence. It might be the folding of proteins. It might be tertiary structure, particularly when [ ] talk[ing] about antibody." Tr. 49:16–19. He continued that "[w]e talk about T cells, its binding of antigen on certain immune genes which can vary between people, including their immune genes. They[are] very hard to define." Tr. 49:19–22.

Despite the fact that Dr. Gershwin's theory of molecular mimicry in this case centers on cytotoxic T cells, Dr. Gershwin acknowledged that "[t]he Gardasil vaccine, interestingly enough, is projected not to induce a lot of cytotoxic CD8 T cells, but there[is] no literature that says it does[not] produce any." Tr. 43:21–24. Dr. Gershwin was "unaware of a single paper that says, you can[not] get CD8 T cells [from HPV vaccination] at all." Tr. 183:13–15. Even if CD8 T cells from HPV vaccination are uncommon, "it could well be that [Petitioner's] problem is that he is the rare individual that does get a CD8 T cell response." Tr. 183:19–21.

On cross-examination, Dr. Gershwin acknowledged that he had seen studies showing that "the HPV vaccine is not designed to produce CD8 T cells, and that[is] why [he] said it could well be the variation here is that this child did make a CD8 response, whereas most people do not." Tr. 79:18–21. He admitted that he did not know of literature measuring CD8 T cell responses to the HPV vaccine. Tr. 79:12–16. He submitted a paper by Stryhn et al.,[32] which examined "$CD8^+$ and $CD4^+$ T cell responses after primary Yellow Fever vaccination . . . ." Pet'r's Ex. 94 at 1, ECF No. 70-2. However, Dr. Gershwin acknowledged that the yellow fever vaccine is a live attenuated vaccine while the HPV vaccine is not. Tr. 80:2–13. Dr. Gershwin acknowledged that he did not provide medical literature showing the CD8 response against any virus that has been associated with alopecia. Tr. 81:1–5. He further stated that he "do[es not] have evidence that any viral infection produces alopecia, and we have very limited data on CD8 T cells and alopecia anyway." Tr. 81:5–8.

Dr. Gershwin submitted a number of papers, including case reports and epidemiological studies, to support his contention that the HPV vaccine Petitioner received can cause AA. He submitted a paper by Wise et al.,[33] discussing sixty reports of hair loss following various

[31] An epitope, or antigenic determinant, is "a site on the surface of an antigen molecule to which a single antibody molecule binds[.]" *Dorland's* at 495.
[32] Anette Stryhn et al., *A Systematic, Unbiased Mapping of $CD8^+$ and $CD4^+$ T Cell Epitopes in Yellow Fever Vaccinees*, 11 FRONTIERS IN IMMUNOLOGY 1836 (2020).
[33] Robert P. Wise, et al., *Hair Loss After Routine Immunizations*, 278 JAMA 1176 (1997).

vaccinations, but primarily hepatitis B vaccinations, identified through the Vaccine Adverse Event Reporting System ("VAERS"). Pet'r's Ex. 79 at 1, ECF No. 24-2. However, "[t]he extent and duration of hair loss varied widely among [thirty-seven] reports with sufficient data to classify." *Id.* at 2. The authors also noted that "the FDA has learned of fewer than [five] cases per year during a decade in which Americans received roughly [one] billion vaccine doses." *Id.* at 3. Because the paper was published in 1997, it did not include data on the HPV vaccine. Tr. 73:2–5. Nevertheless, Dr. Gershwin wrote that Wise et al.'s data "suggest[s] that HPV is the most likely initiating immunogen herein." Pet'r's Ex. 7 at 5.

Dr. Gershwin also submitted a case report by Gallo et al.[34] describing a thirty-one-year-old man who reported hair loss beginning the day after his second COVID-19 vaccination and who was diagnosed with AA. Pet'r's Ex. 93 at 1–2, ECF No. 70-1. Dr. Gershwin discussed a set of nine case reports of AA following COVID-19 vaccination by Scollan et al.[35] Pet'r's Ex. 98, ECF No. 70-6. The approximate time between vaccination and the alopecia flare ranged from one to two weeks following the first dose to four months after the second dose. *Id.* at 2. Dr. Gershwin submitted a case report by Chu et al. [36] of a three-year-old boy who experienced one episode of AA following one week following a third dose of a Japanese encephalitis vaccination and a second episode three days after the third dose of an influenza vaccination. Pet'r's Ex. 95 at 1, ECF No. 70-3. He also discussed an article by Tuccori et al.[37] discussing two case reports of telogen effluvium[38] following receipt of the bivalent HPV vaccine. Pet'r's Ex. 99 at 1, ECF No. 70-7. Dr. Gershwin stated that telogen effluvium is similar to AA. Tr. 58:19–20. He opined that telogen effluvium "likely involves innate immune mechanisms and . . . is immunological in nature, but it[is] not as common as [AA] and not as well studied." Tr. 79:4–7.

Dr. Gershwin explained that he submitted this literature "to point out that the many [sic] people are tuned into the possibility that alopecia can be ascribed to environmental factors, including vaccination." Tr. 57:15–25. Dr. Gershwin testified that these case reports support his opinion that Petitioner's Gardasil vaccination caused his AA. Tr. 58:23–59:1. Respondent's counsel asked Dr. Gershwin about various case reports he submitted, and Dr. Gershwin opined that molecular mimicry most likely caused alopecia in these case reports. Tr. 71:10–18.

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[34] Guiseppe Gallo et al., *Alopecia areata after COVID-19 vaccination*, 11 CLIN EXP VACCINE RES 129 (2022).

[35] Margaret E. Scollan et al., *Alopecia areata after SARS-CoV-2 vaccination*, JAAD CASE REPORTS 2022 https://doi.org/10.1016/j.jdcr.2021.11.023.

[36] Chien-Ho Chu et al., *Alopecia Areata After Vaccination: Recurrence with Rechallenge*, 33(3) PEDIATRIC DERMATOLOGY e218 (2016).

[37] Marco Tuccori et al., *Telogen Effluvium following Bivalent Human Papillomavirus Vaccine Administration: A Report of Two Cases*, 224 DERMATOLOGY 212 (2012).

[38] Telogen effluvium is "the early, excessive, temporary loss of club hairs from normal resting follicles in the scalp as a result of traumatization by some stimulus (e.g., after surgery or childbirth; with starvation, side effects of drugs, traction on hair, high fever, or certain diseases; or with psychogenic stress)." *Dorland's* at 589.

Petitioner submitted a paper by Tu et al.[39] "investigat[ing] the correlation between a history of [HPV] infection and [AA] risk." Pet'r's Ex. 102 at 1. Tu et al. noted that previous studies and reports had associated viral agents and vaccinations with AA, and they indicated that reports of AA following vaccinations "may be caused by a hypersensitive reaction to vaccines, including activation of IFN-γ-producing cells while antigen presentation in the secondary lymphoid tissues in [AA] predisposed patients [ ]." *Id.* at 2. The authors noted that there are more than 600,000 new HPV infections per year worldwide and that HPV is the primary cause of nearly all cervical cancers and is related to other cancers. *Id.* While HPV can cause cancer, "under immunological surveillance of mainly effector T cells, most HPV infections undergo spontaneous clearance within 1–2 years [ ]." *Id.* The authors relied on Taiwan's National Health Insurance Research Database to construct this study. *Id.* at 4. They identified patients who had been diagnosed with HPV between 2000 and 2012 using ICD-9 codes. *Id.* They selected patients with at least one inpatient admission or three outpatient visits to be a part of the study, and they excluded patients who did not receive HPV-related treatment procedures in the three months following HPV diagnosis. *Id.* They included 30,001 subjects in the HPV group and the same number in the control group. *Id.* The authors followed each subject "until the presence of [AA], missing, death, or the end of the study (31 Dec 2013)." *Id.* Tu et al. "discovered a 155% increased risk of developing new-onset [AA] among HPV infected patients, compared with matched controls." *Id.* at 6. They noted that this "risk was significant in both genders and prominent in those aged more than 50 years, followed by 41-50 years old group, 18-30 years old group, and 31-40 years old group." *Id.* They also indicated that "[m]ental disordered patients were prone to develop [AA] in HPV infected patients." *Id.* Tu et al. wrote that "[t]he underlying mechanism that HPV infection increases the risk of developing [AA] remains unclear[, but they] propose[d] the probabilities of chronic inflammation and elevated IFN-γ induced by host immune response against HPV infection, causing immune cell infiltration and cytokine release that will damage immune privilege of hair follicles, and later contribute to alopecia." *Id.* Although the authors stated that they "have provided ample evidence for this positive association [of AA] among HPV symptomatic infection[,]" they acknowledged "[s]everal limitations" in their findings. *Id.* at 7. They noted that "epidemiologic evaluation of HPV infection was challenging, as many infections were not clinically recognized. Using retrospective, ICD-9 based methods to select study groups of HPV infection might have election bias." *Id.* at 8. They acknowledged the possibility of false-positive cases but excluded patients who did not receive treatment to mitigate this concern. *Id.* Because this was a "mono-country evaluation," Tu et al. noted that their "findings may not be applicable to non-Asian ethnic groups." *Id.* They indicated that they did not have data on whether the participants received HPV vaccinations and how this may have impacted their immune systems, and they noted that their findings were solely based on epidemiological evidence. *Id.*

Dr. Gershwin testified that he submitted the Tu et al. study to show that in "at least one study, infection has been linked to the development of alopecia[] . . . ." Tr. 45:20–25. When Respondent's counsel asked about the Tu et al. study, Dr. Gershwin acknowledged that Petitioner is not Taiwanese, but he noted that this does not necessarily mean Petitioner does not have the same HLA alleles as the Taiwanese study subjects. Tr. 68:7–22. Dr. Gershwin acknowledged that this paper has multiple limitations and that it does not indicate whether people developed AA soon

[39] Ting-Yu Tu et al., *Human papillomavirus symptomatic infection associated with increased risk of new-onset alopecia areata: A nationwide population-based cohort study*, 119 J. AUTOIMMUNITY 102618 (2021).

after HPV infection. Tr. 69:22–70:1. Dr. Gershwin opined that autoimmune diseases likely "involve more than one mechanism at any given point in time." Tr. 45:16–19. He noted that the etiology of most autoimmune diseases is unknown, but "infection is still first on the list of virtually anyone that looks at the etiology of autoimmunity." Tr. 45:10–15.

Petitioner filed additional articles to show that AA has been linked to infection in general. He filed a letter to the editor by Nguyen and Tosti,[40] who "conducted an online questionnaire among patients with AA to better understand the relationship between AA and COVID-19." Pet'r's Ex. 103 at 1, ECF No. 81-1. Of 152 respondents, fifty-nine reported a positive COVID test, and twenty-five reported AA symptoms post infection. *Id.* He submitted a review of nine case reports by Christensen and Jafferany,[41] who concluded that AA "may be a dermatologic manifestation of COVID-19, with cases most often appearing [one] to [two] months following infection." Pet'r's Ex. 104 at 2, ECF No. 81-2. Petitioner submitted a review by Nguyen and Tosti[42] that included 1826 patients with hair loss and COVID-19. Pet'r's Ex. 105 at 1, ECF No. 81-3. 143 patients had AA, specifically, but 136 out of those 143 patients had preexisting AA. *Id.* at 1, 4. He submitted a paper by Birkett et al.,[43] who wrote that "AA can be triggered by viral infections such as influenza, [CMV], and the Epstein-Barr virus[]" and discussed eighteen patients with AA which was "thought to have been triggered by either COVID-19 vaccination or COVID-19 infection." Pet'r's Ex. 107 at 1, ECF No. 81-5. He filed an article by Wei et al.[44] on hair loss following dengue virus infection, but the paper does not mention AA specifically. *See generally* Pet'r's Ex. 108, ECF No. 81-6. Petitioner also submitted a case report linking COVID-19 infection and AA. Pet'r's Ex. 109, ECF No. 81-7.[45]

Dr. Gershwin discussed various difficulties in decisively establishing that the HPV vaccine can cause AA via molecular mimicry. He acknowledged that his "theory can[not] be proven at the clinical bench." Tr. 44:19–20. He noted that the best way to prove this theory would be to find immune cells that react with Petitioner's hair follicles, but "the time to identify [these cells] would have had to have been very early on during this disease course, and it would have been a research effort." Tr. Tr. 44:20–45:6. This is because autoimmunity "may go from an adaptive response[] . . . to perpetuation of inflammation where it just persists on its own through innate immune mechanisms." Tr. 44:24–45:2. He "admit[ted] that [his] thesis is entirely based on the mechanism here that it is cytotoxic T cells, amongst other cells, that react with the hair follicle." Tr. 50:11–14. He continued that "their appearance within [fourteen] days is what one would expect of a T cell response, and alopecia is thought to be a T cell response." Tr. 50:14–17. He opined that this is

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[40] Betty Nguyen & Antonella Tosti, *Alopecia areata after COVID-19 infection and vaccination: A cross-sectional analysis*, J. EUR ACAD DERMATOL VENEREOL (2022).
[41] Rachel E. Christensen & Mohammad Jafferany, *Association between alopecia areata and COVID-19: A systematic review*, 7 JAAD INTERNATIONAL 57 (2022).
[42] Betty Nguyen & Antonella Tosti, *Alopecia in patients with COVID-19: A systematic review and meta-analysis*, 7 JAAD INTERNATIONAL 67 (2022).
[43] Liam Birkett et al., *Possible Associations Between Alopecia Areata and COVID-19 Vaccination and Infection*, AESTHETIC SURGERY J. (2022).
[44] Kai-Che Wei et al., *Dengue Virus Infects Primary Human Hair Follicle Dermal Papilla Cells*, B FRONTIERS IN CELLULAR & INFECTION MICROBIOLOGY 268 (2018).
[45] Paul Sgubbi et al., *Alopecia areata in a patient with SARS-Cov-2 infection*, 33 DERMATOLOGIC THERAPY e14295 (2020).

"deeper than just a temporal association[because there is also a] cellular and a mechanistic explanation for the temporal events . . . ." Tr. 50:18–23.

Discussing the medical literature he submitted, Dr. Gershwin explained that he submitted the Stryhn et al. paper to show "how difficult it is[]" to study molecular mimicry. Tr. 52:12–15. The authors were "trying to define reactivity at the yellow fever vaccination, to define the epitopes that these T cells react with." Tr. 52:15–17. However, Dr. Gershwin noted that researchers would "have to look at hundreds of thousands of T cell responses, or at least be able to do this type of sophisticated mapping in only those patients who developed alopecia following a vaccination." Tr. 52:24–53:2. He emphasized that "understanding what[is] called epitopes or structure is not only important for understanding the host's reaction but even in designing vaccines, meaning it[is] still a major research effort" involving antibodies as well as T cells. Tr. 53:6–16. He noted that a follicle is "an organelle which likely has as many [sic] proteins in there," and this makes it difficult to understand "exactly what[is] happening at the molecular level." Tr. 54:18–21. He further wrote in his second expert report that AA "appears to be a T cell disease, and it has been a major challenge to identify T cell epitopes." Pet'r's Ex. 81 at 2, ECF No. 32-1. He averred that "any discussion of etiology and association with vaccines must take into account that it is thus far impossible to individually predict T cell epitopes unique to a specific individual in response to a vaccine." *Id.* He asserted that alopecia "clearly requires environmental stimulation[,]" and he "submit[ted] that the environmental stimulation herein was the HPV vaccine . . . ." *Id.*

Dr. Gershwin explained that he is not relying on a homology to support his theory in this case because he does not "even know what the structure are [sic] of the follicles, because it[is] a complicated organelle of multiple structures." Tr. 89:3–10. However, he testified that molecular mimicry is "the only logical explanation." Tr. 89:11–12. He explained that it is a logical explanation because "you find T cells that are cytotoxic in the area of the follicle when you do immunohistochemistry, and in order for T cells to be there, they have to be there, recognizing antigen. And that antigen is in the follicle and the follicle is what[is] destroyed." Tr. 89:13–19. He stated that this mechanism could apply to any vaccine that can cause alopecia. Tr. 89:20–23. When asked whether it is a fair criticism that he has not identified mimics or a homology, Dr. Gershwin maintained that showing specific mimics is "not plausible" in this case. Tr. 55:23–56:3.

Dr. Gershwin also discussed the difficulty in linking AA to vaccination via epidemiological studies, particularly retrospective studies. Dr. Gershwin noted that identifying a connection would likely require "a large probably multi-national prospective study." Tr. 59:5–16. He stated that "for diseases as uncommon as [AA], one cannot rely on epidemiology because the power calculations are insufficient to provide the necessary data to draw statistical conclusions." Pet'r's Ex. 81 at 2. On cross-examination, Dr. Gershwin opined that finding HPV vaccine-caused AA in an epidemiological study would likely require "boys of [Petitioner's] age, immunized in a cohort population likely in the millions." Tr. 66:7–17. Dr. Gershwin explained that it is easier to identify rare adverse effects when a large number of people are "vaccinated almost at the same time." *See* Tr. 66:18–67:12. He noted that there might not be any cases of AA found if one million boys Petitioner's age received the HPV vaccine. Tr. 67:13–16.

He maintained that Petitioner "developed alopecia because of his unique genetic susceptibility." Pet'r's Ex. 7 at 5. Dr. Gershwin admitted on cross-examination, that there is no

evidence in Petitioner's medical records that he had a unique genetic susceptibility. Tr. 83:10–13. However, Dr. Gershwin maintained that such testing "would be research efforts, and even for a disease like lupus that we know has a genetic basis, we do[not] test" for genetic susceptibility. Tr. 83:13–16. Citing a study involving the measles vaccine, Dr. Gershwin wrote that "it was noted that vaccination induced upregulation of [eighty] different genes[.]" Pet'r's Ex. 7 at 5 (citing Pet'r's Ex. 78 at 1, ECF No. 24-1).[46] Dr. Gershwin stated that "[i]f one considers the number of genetic variations . . . within a gene, then the multitude of genetic diversity in response to a vaccine is truly extraordinary." *Id.* Dr. Gershwin asserted that such genetic diversity "would lead to rare events that would be below the level of detection of epidemiologic analysis." *Id.*

Further discussing the time between Petitioner's vaccination and AA onset, Dr. Gershwin noted that the production of T cells, including CD8 cells and other T cells, would be produced "within a period of three days to about three or four weeks" following a vaccination. Tr. 43:25–44:4. He noted that he would not "make an immunological association" between Petitioner's vaccination and alopecia if the onset of his hair loss was six to eight weeks post vaccination or within twenty-four hours of vaccination. Tr. 44:5–9. Likewise, in his expert report, Dr. Gershwin "emphasized that kinetics of appearance of cytotoxic T cells after vaccination can occur within several days [ ]." Pet'r's Ex. 7 at 4. (citing Pet'r's Ex. 68, ECF No. 23-1).[47] Thus, Dr. Gershwin concluded that "[o]nset within [fourteen] days would certainly be consistent with generation of a CD8 response." *Id.* He averred that Petitioner's HPV vaccination was "[t]he only immunological challenge within that window[.]" *Id.* When asked by Respondent's counsel what a reasonable time frame would be for someone to develop AA through molecular mimicry following vaccination, Dr. Gershwin testified, that "based on data in 2022, [he] think[s] that it would primarily be a T cell reaction, although there may be some natural killer T cell lineages as well. And [he] think[s] it would probably be anywhere from about three weeks to about three, four, five, maybe even six weeks." Tr. 70:12–22.

Dr. Gershwin explain that his theory "fits quite well" with the timing of the onset of Petitioner's AA. Tr. 56:16–18. Dr. Gershwin noted that "there are other cell populations that people have . . . incriminated. They might be involved in hair loss as well. They may have taken longer to develop." Tr. 56:19–21. He continued that "[t]here are those who postulate there should be an innate immune response as well, but [he] think[s] cytotoxic T cells, at least now in 2022, are the most likely . . . candidate for the predominant involvement." Tr. 56:21–25. He noted that "different lineages of cytotoxic T cells [are] being defined, and . . . that field is still in its infancy as well." Tr. 56:25–57:2

Although Dr. Gershwin noted that environmental factors are involved in AA, he did not identify environmental factors that could have contributed to Petitioner's AA besides the vaccination. Tr. 57:3–11. Dr. Gershwin noted that Petitioner suffered from a strep infection on March 8, 2016, but Dr. Gershwin did not believe that this infection contributed to Petitioner's AA.

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[46] Neelam Dhiman et al., *Immune Activation at Effector and Gene Expression Levels After Measles Vaccination in Healthy Individuals: A Pilot Study*, 66 HUMAN IMMUNOLOGY 1125 (2005).

[47] Hannah Rabenstein et al., *Differential Kinetics of Antigen Dependency of CD4$^+$and CD8$^+$ T Cells*, 192 J. IMMUNOL 3507 (2014).

Pet'r's Ex. 7 at 5. In support, Dr. Gershwin cited a paper by Morales-Sánchez et al.,[48] who concluded that an association between throat carriage of bacterial pathogens and AA "appears valid for patients with less than 25% hair loss and a course of disease under [one] year." Pet'r's Ex. 7 at 5; Pet'r's Ex. 80 at 1, ECF No. 24-3.

During my questioning, I asked Dr. Gershwin how he would look for evidence of the immune reaction he proposed in this case. Tr. 84:5–7. He explained that, if he had the facilities and research efforts, he would look for this reaction while it is happening by isolating infiltrating cells from tissues and identifying the cells as "predominantly CD8 cells." Tr. 84:8–15. Then, "[i]n the perfect world, [he] would be able to grow in vitro the cells of his hair follicle, and in the perfect world, be able to show a cytotoxic reaction between his T cells and the cells [ ] growing in the culture." Tr. 84:15–18. He explained that the clinical presentation accompanying this reaction "would be the same . . . as anyone else with this form of acute autoimmune alopecia." Tr. 84:19–22. He explained that there would be no way to distinguish between vaccine-caused and idiopathic alopecia unless he could show that "the same cells that are infiltrating his scalp were cross-reactive with an antigen present in the vaccine or perhaps a neoantigen created during antigen processing of that vaccine." Tr. 84:23–85:5.

Dr. Gershwin agreed that it was fair to say that AA totalis is years in the making. Tr. 87:1–3. He explained that "the reason for that is that in those diseases that take months to years to develop, we can find autoantibody present . . . long before the onset of a disease, whereas in [AA], because we[are] not talking about an autoantibody but rather a pathogenic cytotoxic T lymphocyte is present at the time of the disease development." Tr. 87:3–9. He clarified that diseases that allow the identification and measurement of autoantibodies are less likely to occur due to molecular mimicry. Tr. 87:10–15. He explained that the difference between diseases involving autoantibodies and cytotoxic T cells is that "when you have a disease caused by T cells, the overwhelming number of T cells are present in the tissue. They[are] not found in the blood . . . . Pathology is at the local site." Tr. 88:11–17. He opined that AA totalis, rather than AA, results from "just high levels of cytotoxic T cells[that are] homing . . . [and] trafficking" at the hair follicles. Tr. 88:18–20. However, he did not know of any way to determine whether someone would develop AA or AA totalis. Tr. 88:21–89:2.

Dr. Gershwin acknowledged that stress is a potential trigger of AA that a twelve-year-old boy could experience, but he did not think that stress was a likely trigger in this case because of how quickly and severely Petitioner's AA progressed. Tr. 91:13–19. He explained that Petitioner's AA continued long after the alleged cross-reaction occurred likely due to "nonspecific inflammatory perpetuation of a disease." Tr. 91:25–92:20.

When asked to clarify whether there was no evidence of inflammation in Petitioner's alopecia, Dr. Gershwin noted that "[t]here is evidence in alopecia of inflammatory T cells and other cells, and that is inflammation." Tr. 93:2–10. However, he noted that this inflammation is identified "under a microscope." Tr. 93:11–15.

2. Respondent's Expert, Dr. Matloubian

[48] M.A. Morales-Sánchez et al., *Immunization and Bacterial Pathogens in the Oropharynx as Risk Factors for Alopecia Areata,* 101(5) ACTAS DERMOSIFILOGR. 437 (2010).

Dr. Matloubian noted that AA is "the most common cause of alopecia in otherwise healthy children[]" and that its occurrence in a twelve year old "fits within the normal and acceptable demographics for this disease." Resp't's Ex. A at 3 (citing Resp't's Ex. A, Tab 1, ECF No. 29-2).[49] Dr. Matloubian also countered Dr. Gershwin's characterization of AA as an uncommon disease. Resp't's Ex. C at 3. Dr. Matloubian cited the Islam et al. paper, co-authored by Dr. Gershwin, in which Dr. Gershwin and his co-authors described AA as "a relatively frequent disease with prevalence of 0.1%-0.2% worldwide." *Id.* (quoting Pet'r's Ex. 8 at 2). Dr. Matloubian also noted that the authors cited data to conclude that "[o]verall AA seems to account for about 0.7%-3% of all patients in the United States and about 2% in the United Kingdom." *Id.* (quoting Pet'r's Ex. 8 at 2). He noted that AA "is thought to be an immune-mediated disorder of unclear etiology." Resp't's Ex. A at 3 (citing Resp't's Ex. A, Tab 2 at 1, ECF No. 29-3).[50] Although genetic and environmental factors have been proposed to play roles in AA pathogenesis, "very little is known about the environmental stimuli, if any[,] that may be required for development of this disease." *Id.* Dr. Matloubian wrote that "[s]everal factors, such as infections, metabolic toxins, vaccines, and stress have all been postulated to 'trigger' [AA], but none have been established or universally accepted as a culprit." *Id.* (citing Resp't's Ex. A, Tab 3 at 4, ECF No. 29-4).[51] He noted that while AA has been associated with viral infections such as CMV, such associations have not been confirmed by follow-up studies. *Id.* He continued that "[s]imilarly, based on sporadic case reports of [AA] after hepatitis B vaccination, there was some concern regarding a relationship between the two[, but] follow[-]up studies including experiments in a mouse strain predisposed to developing [AA] failed to establish a causal link between hepatitis B vaccine and development of" AA. *Id.* (citing Pet'r's 15 at 7–8, ECF No. 17-8).[52]

Dr. Matloubian noted that some of the external factors potentially involved in AA pathogenesis, such as stress, "do not involve introduction of a foreign antigen or an exogenous (external) immune altering agent [ ]." *Id.* He noted that a number of the articles Petitioner submitted indicated that stress is a potential trigger of AA. *See id.* (citing Pet'r's Ex. 8 at 4; Pet'r's Ex. 9 at 9, ECF No. 17-2;[53] Pet'r's Ex. 26 at 4, ECF No. 18-9;[54] Pet'r's Ex. 28 at 1, ECF No. 19-1;[55] Pet'r's Ex. 29 at 1, ECF No. 19-2;[56] Pet'r's Ex. 47 at 6, ECF No. 20-10).[57] Dr. Matloubian explained that "[t]he hypothesis that stress mediated alterations in the hypothalamic-pituitary-adrenal [ ] axis could result in immune changes that lead to development of [AA] indicates that an infectious agent associated antigen, usually through a hypothesis based on molecular mimicry with self-antigens[,]

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[49] Amos Gilhar et al., *Alopecia Areata*, 366 N ENGL J. MED 1515 (2012).
[50] Andrew G. Messenger, *Clinical manifestations and diagnosis of alopecia areata*, UPTODATE (2018).
[51] C. Herbert Pratt et al., *Alopecia areata*, 3 NAT REV DIS PRIMERS (2017).
[52] K.J. McElwee et al., *What causes alopecia areata?*, 22 EXPERIMENTAL DERMATOLOGY 609 (2013).
[53] Abdullah Alkhalifah et al., *Alopecia areata update*, 62(2) J. AM ACAD DERMATOL 177 (2010).
[54] Taisuke Ito, *Recent Advances in the Pathogenesis of Autoimmune Hair Loss Disease Alopecia Areata*, 128 J. INVEST DERMATOL 1196 (2008).
[55] Petra Clara Arck et al., *Stress Inhibits Hair Growth in Mice by Induction of Premature Catagen Development and Deleterious Perifollicular Inflammatory Events via Neuropeptide Substance P-Dependent Pathways*, 162(3) AM J. OF PATHOLOGY 803 (2003).
[56] Alexandra Katsarou-Katsari et al., *Alopecia areata and Affected Skin CRH Receptor Upregulation Induced by Acute Emotional Stress*, 203 DERMATOLOGY 157 (2001).
[57] Amos Gilhar et al., *Lymphocytes, neuropeptides, and genes involved in alopecia areata*, 117 J. CLIN INVEST 2019 (2007).

may not be playing a role in this disease." *Id.* He noted that "[t]his is consistent with the finding that C3H/HeJ mouse model of [AA] develop the disease spontaneously and in the absence of introduction of an infectious agent or immunization with a foreign peptide [ ]." *Id.* (citing Pet'r's Ex. 66) (emphasis omitted). Because Sundberg et al. were able to increase the incidence of spontaneously occurring alopecia from 0.25% to 20% through inbreeding the mice, Dr. Matloubian opined that this indicates "a very strong role" of genetics in alopecia pathogenesis. *Id.* (citing Pet'r's Ex. 66 at 1). Dr. Matloubian explained that the mice developed spontaneous disease and that "if there was an infectious immunology, you would expect all of the mice in the same cage to have it . . . [y]ou would[not] expect just only [twenty] percent of the colony to have it." Tr. 122:9–18. He stated that "[t]he fact that an external trigger, infectious or otherwise[,] has not been identified in this model [ ] suggests that a disease initiating external cue or stimulus may also not be required for development of [AA] in humans." Resp't's Ex. A at 3. In addition, Respondent filed an article by Maglakelidze et al., [58] which reported "that 62% of C57BL/6J female *Aire* mice spontaneously developed persistent AA-like lesions that displayed several hallmarks of human AA." Resp't's Ex. H at 2, ECF No. 84-3. The researchers found "infiltrate comprised of $CD8^+$ T cells, $CD4^+$ T cells, $CD68^+$ macrophages[] . . . ." *Id.* They explained that "[p]atients with mutations in autoimmune regulator (*AIRE*) are 15x more likely to develop AA than the general population[] . . . ." *Id.*

Dr. Matloubian noted that "given the complex pathogenesis of autoimmune diseases, such as [AA], the research field is moving away from simplistic explanations, such as molecular mimicry[,] due to infection or vaccination, because of a lack of convincing rigorously tested evidence in their support, to other environmental risk factors, such as diet and antibiotic usage that may affect the microbiota." Resp't's Ex. A at 4. Citing a paper by Alkhalifah et al. filed by Petitioner, that notes that dietary soy oil increased resistance to AA in mice, Dr. Matloubian stated that "[s]ince diet has been shown to affect the microbiome, it can thus indirectly perturb the immune system and lead to development of [AA]." *Id.* (citing Pet'r's Ex. 9 at 9). Dr. Matloubian asserted that the microbiome "has been shown to alter immune tolerance through their effects on regulatory T cells[,]"[59] which "maintain immune tolerance and prevent immune activation towards self-antigens." *Id.* Citing a paper by Ali and Rosenblum,[60] he noted that changes in the gut microbiome have been linked "with changes in the numbers and function" of such cells." *Id.* (Resp't's Ex. A, Tab 8, ECF No. 29-9). He continued that regulatory T cells "have been found at the base of hair follicles indicating an important role for them in maintaining tolerance in this specific location." *Id.* (citing Resp't's Ex. A, Tab 8 at 6). He also cited an article by Gilhar et al. that noted that dysfunctional regulatory T cells have been found in diseases such as psoriasis, multiple sclerosis, and autoimmune polyglandular syndrome type 1. Pet'r's Ex. 47 at 5. Gilhar et al. also noted that C3H/HeJ mice with alopecia have been found to have low levels of regulatory T cells in their skin. *Id.* He also cited a paper by Petukhova et al.[61] filed by Petitioner to show that

[58] Natella Maglakelidze et al., *Aire deficiency leads to the development of alopecia areata-like lesions in mice*, J. INVEST DERMATOL (2022).

[59] Regulatory T cells are "a subset of $CD4^+$ T cells that can suppress activity of effector cells such as helper cells and suppressor cells, and inhibit autoimmune diseases." *Dorland's* at 318. CD4 T cells are T cells that "carry the CD4 antigen[.]" *Id.* at 311.

[60] Niwa Ali & Michael D. Rosenblum, *Regulatory T cells in skin*, 152 IMMUNOLOGY 372 (2017).

[61] Lynn Petukhova et al., *Genome-wide association study in alopecia areata implicates both innate and adaptive immunity*, 466 NATURE 113 (2010).

genetic studies of individuals with alopecia "have found 'association with genomic regions containing several genes controlling the activation and regulation of regulatory T cells [ ].'" Resp't's Ex. A at 4 (quoting Pet'r's Ex. 17 at 1, ECF No. 17-10). He concluded that, taken together, "these studies raise the possibility that alteration in regulatory T cell numbers or function could contribute to pathogenesis of [AA]." *Id.* Noting that Petitioner was treated with antibiotics before his vaccination in March of 2016, Dr. Matloubian surmised that "this course of antibiotics [possibly] led to alteration of his gut microbiome, which then led to disruption of regulatory T cell function." *Id.* Citing Ali and Rosenblum, Dr. Matloubian averred that this disruption could result in AA in a genetically-susceptible individual. *Id.* He also cited a report of two cases by Rebello et al.,[62] which he stated "showed that restoration of gut microbiome through a fecal implant in two individuals with [AA] led to hair regrowth without any other treatments." *Id.* (citing Resp't's Ex. A, Tab 9, ECF No. 29-10). One patient, a twenty-year-old man with AA causing 95–99% hair loss, improved to 25–49% hair loss less than two years after the transplant with no other post-transplant treatment besides two steroid injections. Resp't's Ex. A, Tab 9 at 1–3. Dr. Matloubian concluded that, therefore, "a role for the microbiome in affecting hair regrowth is not speculative but has been clearly established in the clinical setting." *Id.*

Citing a review article by Grimaldi-Bensouda et al.,[63] Dr. Matloubian asserted that "multiple studies have not found any association between administration of the quadrivalent [HPV] vaccines, including Gardasil and the development of a variety of autoimmune diseases." Resp't's Ex. A at 5 (citing Resp't's Ex. A, Tab 11, ECF No. 30-2). In addition to noting that several studies had not provided "robust evidence" linking the HPV vaccine to autoimmune diseases, Grimaldi-Bensouda et al. conducted a study of eleven to twenty-five-year-old girls and women in France over six years. Resp't's Ex. A, Tab 11 at 2. They concluded that "[e]xposure to HPV vaccine was not associated with an increased risk of [autoimmune disorders] within the time period studied." *Id.* Dr. Matloubian noted that these studies "did not specifically determine the risk of [AA] after HPV vaccination[]" but rather "evaluate[d] for other associated autoimmune diseases such as systemic lupus erythematosus [("SLE")] and thyroiditis." Resp't's Ex. A at 5. Noting that HPV has been shown in studies to be safe and effective in people with preexisting autoimmune disorders, including SLE, Dr. Matloubian asserted that "[t]his makes the likelihood of an autoimmune disease occurring due to HPV immunization of a genetically predisposed person extremely low." *Id.* (citing Resp't's Ex. A, Tab 12, ECF No. 30-3).[64] Dr. Matloubian concluded that "[i]n the absence of an established and universally agreed upon trigger of any kind for [AA], to implicate the Gardasil vaccine as the cause of [Petitioner's AA] would be quite speculative and not supported by the medical literature." *Id.* at 5–6. Dr. Matloubian noted that although "HPV infections and [AA] are quite common, no association has been recognized between the two." Resp't's Ex. C at 4.

Dr. Matloubian asserted that "none of the 71 articles submitted by Dr. Gershwin [with his first expert report] provide a scientific basis that would support a specific causal relationship

[62] Dionne Rebello et al., *Hair Growth in Two Alopecia Patients after Fecal Microbiota Transplant*, 4 ACG CASE REPORTS J. 1 (2017).
[63] Lamiae Grimaldi-Bensouda et al., *Risk of autoimmune disease and human papillomavirus (HPV) vaccines: Six years of case-referent surveillance*, 79 J. AUTOIMMUNITY 84 (2017).
[64] J. Patricia Dhar, *The safety and immunogenicity of Quadrivalent HPV (qHPV) vaccine in systemic lupus erythematosus*, 35 VACCINE 2642 (2017).

between the antigenic components of the Gardasil vaccine and [AA] through a mechanism based on molecular mimicry." Resp't's Ex. A at 7. Dr. Matloubian averred that molecular mimicry "has rarely been persuasively demonstrated as a major cause of autoimmunity in general, with a few notable exceptions[] . . . ." *Id.* He continued that molecular mimicry "has become a less favorable explanation" as understanding of the immune system has advanced and that it "is definitely not applicable to those autoimmune diseases that are not post-infectious and thus, may not be triggered by exposure to a foreign antigen." *Id.*

Dr. Matloubian explained that "[t]he two arms of the immune system that are implicated in autoimmunity, potentially through molecular mimicry, are B cells and T cells." Resp't's Ex. A at 7. He continued that B cells "make antibodies that are specific for one molecular pattern[]" while T cells "only detect small linear pieces of proteins in the context of HLA molecules[, which] are different between unrelated individuals . . . ." *Id.* He noted that molecular mimicry at the level of B cells would involve specific antibodies while "[f]or a T cell mediated disease, the same T cells that are generated against a specific pathogen-derived peptide seen in the context of an HLA molecule also have to see peptides derived from a self-protein in the context of that same HLA [ ]." *Id.* Dr. Matloubian thus concluded that "for a vaccine to be mechanistically associated with a specific autoimmune disease through molecular mimicry, the pathogen that the vaccine is derived from should also be associated with the same specific autoimmune disease [ ]." *Id.* In support, he cited a paper by Schattner[65] that outlines requirements for connecting vaccinations and autoimmune diseases. *Id.* at 8 (citing Resp't's Ex. A, Tab 13, ECF No. 30-4). Schattner conducted a search of publications between 1996 and 2004 to look for connections between autoimmune manifestations and vaccinations. Resp't's Ex. A, Tab 13 at 1. She found that "[w]henever controlled studies of autoimmunity following viral vaccines were undertaken, no evidence of an association was found." *Id.* However, she acknowledged that "very rare individual patients may develop certain restricted patterns of autoimmune damage following some of the viral vaccines[] . . . ." *Id.* at 8. Based on her findings, Schattner proposed the following guidelines:

> To establish a role for viral vaccines in the subsequent development of autoimmunity or autoimmune diseases[,] several conditions have to be met. *First*, virus infections should be linked to autoimmunity. *Second*, a mechanism or mechanisms whereby exposure to viral antigens (be it during infection or vaccination) leads to autoimmunity must be established. *Third*, evidence must be obtained that patients who have been vaccinated against viruses developed an autoimmune disease, bearing in mind that association alone does not necessarily indicate causality.

Id. at 6.

Dr. Matloubian also cited the Institute of Medicine's ("IOM") reasoning that thrombocytopenia can result from the measles, mumps, rubella ("MMR") vaccine because thrombocytopenia can occur after a measles infection.[66] *Id.* at 9–10. However, Dr. Matloubian emphasized that unlike this association, "there has [sic] been no reports of an association between

[65] Ami Schattner, *Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines*, 23 VACCINE 3876 (2005).
[66] Dr. Matloubian did not cite medical literature to support this contention.

infection with human papilloma virus and development of [AA].” *Id.* at 10. Because “the antigenic components of the Gardasil vaccine are derived from the human papilloma virus” Dr. Matloubian concluded that “it is highly unlikely and biologically implausible that the vaccine can cause [AA] through a mechanism based on molecular mimicry with its genetically encoded components [ ].” *Id.* While Dr. Matloubian acknowledged that certain autoimmune diseases, such as rheumatic heart disease and Guillain-Barré Syndrome (“GBS”), have been found to occur within a short time after certain infections, he also testified that “[m]ost autoimmune diseases have not been established to occur after a specific infection in a short period of time.” Tr. 108:7–109:1.

Dr. Matloubian stated that when he searched for publications associating HPV vaccines with AA, he was unable to find any. Resp’t’s Ex. A at 10. He also discussed the articles submitted by Dr. Gershwin and noted that only a few of them mention molecular mimicry. *Id.* He cited the Madani and Shapiro article filed by Petitioner, in which the authors wrote that “[t]he whole concept of molecular mimicry of the hair follicle with a virus is intriguing, but the evidence for a viral origin of AA at this time is not conclusive.” *Id.* (quoting Pet’r’s Ex. 10 at 4).

Dr. Matloubian noted that “[i]t is important to make the distinction between what causes the damage to the hair follicles, which potentially could be cytotoxic T cells, and the mechanism by which they become activated to do so.” Resp’t’s Ex. C at 4. While he acknowledged that cytotoxic T cells have been associated with AA pathogenesis, he opined that “[t]here is no clear scientific evidence or consensus among researchers that these cells become activated through molecular mimicry with a foreign antigen.” *Id.* He explained that “there are many mechanisms that can lead to loss of T cell or B cell tolerance.” Tr. 107:7–9. Such mechanisms include “escape of autoreactive T cells from the thymus[]”[67] and a defect in a single gene. Tr. 107:9–18.

Dr. Matloubian testified that “T cells can be divided generally into CD8 positive or cytotoxic T cells . . . and CD4 T cells or helper T cells . . . .” Tr. 144:11–14. He explained that CD8 T cells “kill cells that are infected by a virus or other intracellular pathogens.” Tr. 144:15–17. However, CD4 T cells are “really good at seeing extracellular microbes, and the reason for it is that these viruses or proteins that are floating outside or bacteria that are floating outside get picked up by what are called macrophages or dendritic cells.” Tr. 145:9–15. Rather than killing cells through recognizing a peptide specific to a certain infection like CD8 T cells, CD4 T cells “secrete cytokines and activate macrophages to kill these cells.” Tr. 145:3–7, 18–19. Dr. Matloubian asserted that “protein vaccines such as the Gardasil vaccine, they typically get picked up by these macrophages/dendritic cells and predominantly they get presented to CD4 T cells and activate CD4 T cells to MHC class 2.” Tr. 145:21–24. He continued that “it[is] unlikely for them to get presented to CD8 T cells, because the antigens that get presented in the CD8 T cells are usually the ones that are generated in the cytoplasm.” Tr. 146:1–4. He opined that “there are really no papers showing CD8 T cells get activated by the HPV vaccine . . . because they probably do[not] get much activated. That[is] not what the vaccine is designed for.” Tr. 146:9–12. Instead, “[t]he vaccine is designed to activate CD4 T cells so it provides help to B cells . . . And these B cells will now make antibodies to these proteins in the Gardasil vaccine.” Tr. 146:12–16. He noted that if the HPV vaccine was good at promoting cytotoxic T cells, it would be used to treat cervical cancer, which occurs due to HPV infection and contains HPV virus. Tr. 146:19–23. He stated that

[67] The thymus is “a primary lymphoid organ consisting of two pyramidal lobes usually located in the mediastinum.” *Dorland’s* at 1895. It is “the site of production of immunocompetent T lymphocytes.” *Id.*

"if the Gardasil vaccine was good enough to induce cytotoxic T cells, it would be used to vaccinate people who suffer from cervical cancer to be able to activate these cytotoxic T cells to get rid of those [sic] cancer, but it[is] not good enough to do that." Tr. 147:23–148:2. Dr. Matloubian criticized Dr. Gershwin's use of Stryhn et al. paper to support his theory in this case because the yellow fever vaccine, unlike the HPV vaccine, is a live attenuated vaccine. Tr. 148:17–18. He explained that live attenuated vaccines contain "actual infection[] . . . and get inside the cells and replicate, they induce a good cytotoxic T cell response, whereas protein vaccines are not very good at doing that." Tr. 148:19–24.

Dr. Matloubian discussed a paper by Xing et al.[68] filed by Petitioner, in which the "authors show that cytotoxic T cells are involved in a spontaneous mouse model of [AA] . . . ." Resp't's Ex. C at 4 (citing Pet'r's Ex. 67, ECF No. 22-10). Dr. Matloubian noted that the authors "suggest that the T cells may recognize and kill hair follicle cells through expression of NKG2D, a natural killer cell receptor." *Id.* (citing Pet'r's Ex. 67). Dr. Matloubian explained that "[t]he ligands for NKG2D, such as H60 and Rae-1 are expressed on the surface of cells when they become 'stressed' so that natural killer cells or other cytotoxic cells expressing NKG2D can recognize and kill those cells." *Id.* He noted that unlike NKG2D ligands, "[c]omponents of the Gardasil vaccine cannot be processed and expressed on surface of cells" and that thus, "NKG2D expressing cytotoxic T cells cannot be activated through molecular mimicry by components of the Gardasil vaccine." *Id.* at 4–5. He stated that "Dr. Gershwin has not provided any literature to support that this mouse model is based on molecular mimicry, with any cross-reactive T cells." Tr. 123:21–24.

Dr. Matloubian addressed the case reports and similar papers Petitioner submitted. Discussing the Wise et al. paper, Dr. Matloubian noted that the authors "were not looking at [AA] specifically[]" but rather at "this passive report of hair loss after vaccination, and they found only a few cases." Tr. 113:4–8. Noting that the authors' findings were equivalent to a one in twenty million incidence of hair loss following vaccinations, Dr. Matloubian stated that the typical incidence rate of one in 5,000 per year is much higher. Tr. 113:21–114:13 (citing Pet'r's Ex. 79 at 3). He testified that "the point here is that people after vaccination can coincidentally have AA because the rate is so high." Tr. 114:13–14. Regarding the COVID-19 vaccine case reports, Dr. Matloubian explained that coronaviruses are "very different from human papillomavirus[]" in that coronaviruses have an RNA-based genome and a membrane while "human papillomaviruses have DNA as their genome[]" and no membrane. Tr. 114:20–115:5. Dr. Matloubian also noted that in the Gallo et al. case report, the individual developed AA within one day of his second COVID vaccination, which is "not consistent with a mechanism based on molecular mimicry[.]" Tr. 115:6–9 (citing Pet'r's Ex. 93 at 1–2). Discussing the Scollan et al. article, Dr. Matloubian noted that "the COVID mRNA vaccine is not the same as the HPV vaccine which is made of only proteins." Tr. 116:13–19. He also noted some individuals in this study developed hair loss months following their second COVID vaccine doses, which is "not consistent with a mechanism based on molecular mimicry." Tr. 117:2–5 (citing Pet'r's Ex. 98 at 2). Addressing the Chu et al. case report, Dr. Matloubian likewise noted that Japanese encephalitis is a "very different" virus and that the authors proposed a different mechanism. Tr. 115:22–116:4.

[68] Luzhou Xing et al., *Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition*, 20 NATURE MEDICINE 1043 (2014).

Addressing the Tu et al. study, Dr. Matloubian noted that this article did not change his opinion in this case. Tr. 129:24–130:1. He stated that the study is not ideal because it is a "population-based retrospective cohort study" using billing codes from medical records. Tr. 130:6–13. Dr. Matloubian also noted that that there are 200 types of HPV, only forty of which can infect the genital tract. Tr. 131:12–15. He stated that "the infections [Tu et al. are] looking at are not the same HPV [strains as] the four HPV [strains] that were in the Gardasil vaccine." Tr. 131:19–21. He also pointed out that the authors were only looking at symptomatic HPV infections, but most HPV infections are asymptomatic. Tr. 131:21–25. Dr. Matloubian noted that, according to some estimates, "80 up to 100 percent of sexually active individuals have been infected with HPV at some point." Tr. 133:2–4. Dr. Matloubian also explained that when an individual had HPV symptoms, such as warts, does not indicate when she was infected, as she "could have had the infection for many years before that." Tr. 133:24–134:5. Discussing the time between HPV symptoms and AA onset in this study and when differences in incidence occurred between the affected individuals and the control group, Dr. Matloubian, again noted that study participants likely had HPV for years before diagnosis and that this timeline is not consistent with a mechanism based on molecular mimicry. Tr. 134:15–135:7. He noted that Tu et al. "start[ed] seeing a difference between the control group versus not, somewhere between four to six years" after HPV diagnosis. Tr. 134:18–20. He opined that this paper does not show that AA "can happen shortly after an HPV infection." Tr. 140:12–15. Dr. Matloubian noted that AA is common in children, and he cited the Gilhar et al. paper, which identified the median age of AA onset in one study as ten years old. Tr. 140:25–141:3 (citing Resp't's Ex. A, Tab 1 at 1). Because the HPV infections the Gardasil vaccine protects against are uncommon in children, Dr. Matloubian concluded that it is unlikely that HPV infection causes AA in children. Tr. 141:23–25.

Dr. Matloubian disagreed with Dr. Gershwin's contention that Petitioner's AA was likely caused by the HPV vaccine because the HPV vaccine was the only immunological challenge Petitioner experienced in the weeks before his AA onset. Tr. 149:13–17. He opined that "[i]n the absence of any epidemiologic or scientific evidence to link either infection or immunization with [HPV] and the development of [AA], . . . coincidence is the most likely explanation." Resp't's Ex. A at 12. Extrapolating data from a paper by Ahmed et al.,[69] Dr. Matloubian noted that "if 10,000 individuals receive the Gardasil vaccine, there is a 90% chance that one individual will develop [AA] through coincidence alone based on its annual incidence." *Id.* (citing Resp't's Ex. A, Tab 10). He noted that "based on the literature provided by Dr. Gershwin[,] it appears that some experts believe that internal causes, such as changes in the microbiome, random gene expression, or even hormonal changes that can occur, especially in a 12-year-old who is undergoing puberty can result in immune changes and development of [AA]." *Id.* Dr. Matloubian concluded that Dr. Gershwin "is relying solely on temporal relationship between vaccination and development of disease." *Id.* He disagreed with Dr. Gershwin's contention that an examination of one million people who received the HPV vaccine might not reveal a single case of AA. Tr. 151:10–13. Dr. Matloubian explained, "[y]ou will see a lot, but that[is] because of coincidence alone." Tr. 151:13–14. Dr. Matloubian indicated that the range of time frames between vaccination and AA onset presented in the case reports submitted by Petitioner "does[not] seem to support a unified theory based on molecular mimicry." Tr. 163:5–9. However, he agreed that CD8 positive T cells can activate and cause dysfunction within one to two weeks. Tr. 164:11–15.

[69] S. Sohail Ahmed et al., *Assessing the Safety of Adjuvanted Vaccines*, 3(93) VACCINES 1 (2011).

IV. Applicable Legal Standards

To receive compensation under the Vaccine Act, a petitioner must demonstrate either that: (1) the petitioner suffered a "Table injury" by receiving a covered vaccine and subsequently developing a listed injury within the time frame prescribed by the Vaccine Injury Table set forth at 42 U.S.C. § 300aa-14, as modified by 42 C.F.R. § 100.3; or (2) that petitioner suffered an "off-Table injury," one not listed on the Table, as a result of his receiving a covered vaccine. *See* 42 U.S.C. §§ 300aa-11(c)(1)(C); *Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1319–20 (Fed. Cir. 2006). Petitioner does not allege a Table injury in this case; thus, he must prove that his injury was caused-in-fact by a Table vaccine.

To establish causation-in-fact, a petitioner must demonstrate by a preponderance of the evidence that the vaccine was the cause of the injury. 42 U.S.C. § 300aa-13(a)(1)(A). A petitioner is required to prove that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321–22 (quoting *Shyface v. Sec'y of Health & Hum. Servs.*, 165 F.3d 1344, 1352–53 (Fed. Cir. 1999)).

In the seminal case of *Althen v. Sec'y of the Dept. of Health & Hum. Servs*, the Federal Circuit set forth a three-pronged test used to determine whether a petitioner has established a causal link between a vaccine and the claimed injury. *See* 418 F.3d 1274, 1278–79 (Fed. Cir. 2005). The *Althen* test requires petitioners to set forth: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278. To establish entitlement to compensation under the Program, a petitioner is required to establish each of the three prongs of *Althen* by a preponderance of the evidence. *Id.* "[C]lose calls regarding causation are resolved in favor of injured claimants." *Id.* at 1280. Further, evidence used to satisfy one prong of the test may overlap to satisfy another prong. *Capizzano*, 440 F.3d at 1326.

A petitioner who satisfies all three prongs of the *Althen* test has established a prima facie showing of causation. *Hammitt v. Sec'y of Health & Hum. Servs*., 98 Fed. Cl. 719, 726 (2011). A petitioner who demonstrates by a preponderance of the evidence that he suffered an injury caused by vaccination is entitled to compensation unless the respondent can demonstrate by a preponderance of the evidence that the injury was caused by factors unrelated to the vaccination. *See Althen*, 418 F.3d at 1278; *Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d 543, 547 (Fed. Cir. 1994). In such a case, the government must not merely prove the existence of an alternative cause, but that such an alternative actually caused the injury. *Knudsen*, 35 F.3d at 549. Consequently, when and if the petitioner establishes a prima facie case, the burden then shifts to the government to prove that an alternative cause, unrelated to the administration of the vaccine, was the "sole substantial factor" in causing the alleged injury. *See de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1354 (Fed. Cir. 2008); *see also Hammitt*, 98 Fed. Cl. at 726 (explaining that the respondent's burden is to show that the "factor unrelated" was the "sole substantial factor" in causing the injury). Additionally, a factor unrelated "may not include 'any idiopathic, unexplained, unknown, hypothetical, or undocumentable cause, factor, injury, illness

or condition.'" 42 U.S.C. § 300aa-13(a)(2); *see also Doe v. Sec'y of Health & Hum. Servs.*, 601 F.3d 1349 (Fed. Cir. 2010) (stating that an idiopathic diagnosis cannot be a "factor unrelated," as it is idiopathic).

V. Discussion

A. *Althen* Prong One

Under the first prong of *Althen*, a petitioner must offer a scientific or medical theory that answers in the affirmative the question: "can the vaccine[] at issue cause the type of injury alleged?" *See Pafford v. Sec'y of Health & Hum. Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *mot. for rev. denied*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352 (Fed. Cir. 2006). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548. Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 548–49. Petitioners are not required to identify "specific biological mechanisms" to establish causation, nor are they required to present "epidemiologic studies, rechallenge[] the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities." *Capizzano*, 440 F.3d at 1325 (quoting *Althen*, 418 F.3d at 1280). Scientific and "objective confirmation" of the medical theory with additional medical documentation is unnecessary. *Althen*, 418 F.3d at 1278–81; *see also Moberly*, 592 F.3d at 1322. However, as the Federal Circuit has made clear, "simply identifying a 'plausible' theory of causation is insufficient for a petitioner to meet her burden of proof." *LaLonde v. Sec'y of Health & Hum. Servs.*, 746 F.3d 1334, 1339 (Fed. Cir. 2014) (citing *Moberly*, 592 F.3d at 1322). Indeed, the Federal Circuit has "consistently rejected theories that the vaccine only 'likely caused' the injury and reiterated that a 'plausible' or 'possible' causal theory does not satisfy the standard." *Boatmon v. Sec'y of Health & Hum. Servs.*, 941 F.3d 1351, (Fed. Cir. 2019) (citing *Moberly*, 592 F.3d at 1322 and *LaLonde*, 746 F.3d at 1339). Rather, "[a] petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case." *Moberly*, 592 F.3d at 1322. In general, "the statutory standard of preponderance of the evidence requires a petitioner to demonstrate that the vaccine more likely than not caused the condition alleged." *LaLonde*, 746 F.3d at 1339.

Furthermore, establishing a sound and reliable medical theory connecting the vaccine to the injury often requires a petitioner to present expert testimony in support of her claim. *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357,1361 (Fed. Cir. 2000). The Supreme Court's opinion in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), requires that courts determine the reliability of an expert opinion before it may be considered as evidence. However, in the Vaccine Program, the *Daubert* factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 53, 66–67 (2010) ("[U]niquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted."); *see also Cedillo v. Sec'y of Health & Hum. Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). Under *Daubert*, the

> factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community.

Terran, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592–95).

The *Daubert* factors are "meant to be helpful, not definitive." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 151 (1999). The factors do not "constitute 'a definitive checklist or test'" and may be applied differently depending on the facts of a particular case. *Id.* at 150 (quoting *Daubert*, 509 U.S. at 593).

"In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." *Daubert*, 509 U.S. at 590 (citation omitted). Thus, for Vaccine Act claims, a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly*, 592 F.3d at 1324. Nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder v. Sec'y of Health & Hum. Servs.*, 88 Fed. Cl. 706, 743 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)); *see also D'Tiole v. Sec'y of Health & Hum. Servs.*, No. 15-085V, 2016 WL 7664475, at *24 (Fed. Cl. Spec. Mstr. Nov. 28, 2016) (stating that the Vaccine Act "require[s] a chain of reliable propositions supporting [a] petitioner's theory[]").

Petitioner's proposed theory of molecular mimicry has two central components. The first component is that Petitioner "received a vaccine that produced cytotoxic T cells[.]" Pet'r's Ex. 7 at 5. The second is that these cytotoxic T cells "were directed at his hair follicles and [ ] cross react[ed] with an epitope or region of the Gardasil vaccine." *Id.* Accordingly, to demonstrate that this theory is sound and reliable by a preponderant standard, Petitioner must present preponderant evidence that the HPV vaccine he received "produce[s] cytotoxic T cells." Petitioner cannot prevail on Prong One because he has failed to present such evidence.

Despite filing ninety-seven pieces of medical literature, Petitioner has not filed a single article indicating that the HPV vaccine can or does produce cytotoxic T cells. While Petitioner does not need to rely on medical literature specifically to support his theory, he must still provide some form of preponderant evidence that his proposed mechanism can or does occur. Petitioner's own expert, Dr. Gershwin, admitted that "the HPV vaccine is not designed to produce CD8 T cells[.]" Tr. 79:18–21. Likewise, Dr. Matloubian explained that protein vaccines like Gardasil are designed to activate CD4 T cells rather than cytotoxic T cells. Tr. 146:9–16. Dr. Matloubian noted that "there are really no papers showing CD8 T cells get activated by the HPV vaccine . . . because they probably do[not] get much activated." Tr. 146:9–12. Dr. Matloubian supported his point by noting that if the HPV vaccine induced cytotoxic T cells, it would be used to treat cervical cancer, which is often caused by the HPV strains that Gardasil is designed to protect against, via activation of cytotoxic T cells against the HPV in the cancer cells. *See* Tr. 146:19–23. He further explained that while Petitioner filed the Stryhn article, which indicates that the yellow fever vaccine can

produce cytotoxic T cells, the yellow fever vaccine is a live attenuated vaccine. Tr. 148:17–18. It contains "actual infection," and it "induce[s] a good cytotoxic T cell response[;] whereas protein vaccines[, such as Gardasil,] are not very good at doing that." Tr. 148:19–24. Rather than presenting evidence that the Gardasil vaccine induces cytotoxic T cells, Dr. Gershwin asserted that that there is "no literature that says [the Gardasil vaccine] does[not] produce any [cytotoxic T cells]." Tr. 43:21–24. He claimed that "it could well be that [Petitioner's] problem is that he is the rare individual that does get a CD8 T cell response." Tr. 183:19–21. Thus, Petitioner's response to the dearth of evidence supporting a central component of his theory appears to be that it is theoretically *possible* that the HPV vaccine *could* induce a CD8 T cell response in some people. However, showing that this response is merely possible is insufficient to sustain this essential component of Petitioner's theory by preponderant evidence. *See, e.g.*, *Canuto v. Sec'y of Health & Hum. Servs.*, 660 Fed. Appx. 955, 957 (Fed. Cir. 2016) (citing *W.C. v. Sec'y of Health & Hum. Servs.*, 704 F.3d at 1356 (Fed. Cir. 2013) ("[T]he petitioner must do more than demonstrate a 'plausible' or 'possible' causal link between the vaccination and the injury[.]"). Petitioner has failed to provide preponderant evidence that this response actually can occur.

In *Cordova v. Sec'y of Health & Hum. Servs.*, in which Dr. Gershwin was also the petitioner's expert, the chief special master concluded that the petitioner failed to present preponderant evidence that the HPV vaccine could cause AA via the upregulation of cytotoxic T cells. He reached this conclusion in part because "there [was] an overarching deficiency in Dr. Gershwin's contentions about the capacity of the HPV vaccine to cause an upregulation of the cytotoxic T cells central to hair follicle destruction." No. 17-1282V, 2021 WL 3285367, at *18 (Fed. Cl. Spec. Mstr. June 21, 2021). The chief special master wrote that "[a]lthough it is not disputed that CD8+ T cells are central to AA's progression, few reliable articles stand for the proposition that the HPV vaccine causes the upregulation of this T cell in sufficient amounts to be pathologic." *Id.* Unlike in the present case, the petitioner in *Cordova* presented "a few small-scale studies aimed at evaluating the immunogenicity of the HPV vaccine, noting that they suggest some increased T cell upregulation after receipt of the vaccine." *Id.* at *17. The chief special master found that the articles did not show that the increase in T cells "(a) is likely causal of AA, or (b) even involves the specific kind of cytotoxic T cells that drive AA." *Id.* While the petitioner in *Cordova* was unsuccessful, he at least provided some evidence linking the HPV vaccine to a T cell response, although not to a cytotoxic T cell response specifically. Thus, Petitioner's evidence to support that the HPV vaccine can induce cytotoxic T cells is even weaker in this case. As in *Cordova*, Petitioner has failed to present preponderant evidence of this component of his theory.

Furthermore, even if the HPV vaccine could induce a pathologic cytotoxic T cell response, Petitioner has failed to demonstrate by preponderant evidence the second component of his theory, that such a response could destroy immune privilege of the hair follicle to cause AA. Although Program petitioners often present homologies between vaccine components and human tissues, such is not required to present preponderant support for a theory of molecular mimicry. However, petitioners must present some form of preponderant evidence that a cross reaction between the vaccine and body part at issue can occur. Indeed, "[p]etitioners cannot simply invoke the concept of molecular mimicry and call it a day . . . Rather, they need to offer *reliable* and persuasive medical or scientific evidence of some kind . . . that suggests the vaccine components could interact with self structures as maintained." *Johnson v. Sec'y of Health & Hum. Servs.*, No. 14-254V, 2018 WL 2051760, at *26 (Fed. Cl. Spec. Mstr. Mar. 23, 2018). As in *Cordova*, "Petitioner lacks

evidence suggesting an association between the HPV vaccine and AA, whether in the form of literature[,] . . . studies[,] or testimony from Dr. Gershwin derived from his own research or treatment experience." *Cordova*, 2021 WL 3285367, at *16.

Petitioner submitted some case reports and papers to establish a relationship between vaccines, including HPV, and conditions that involve hair loss, including AA. The Tuccori et al. case reports center on the bivalent HPV vaccine, which is not the same type of HPV vaccine Petitioner received, and telogen effluvium, which is not AA. *See* Pet'r's Ex. 99. This is the only article Petitioner filed that links any HPV vaccine and hair loss. However, it does not provide persuasive evidence of a link between HPV vaccines and AA because the article draws from a small number of cases and involves a different type of hair loss. *See Al-Uffi vs. Sec'y of Health & Hum. Servs*., No. 13-956V, 2017 WL 1713113 at *16 (Fed. Cl. Spec. Mstr. Feb. 22, 2017) ("Individual case studies are not themselves particularly probative in the context of establishing the first *Althen* prong (especially where they involve a totally different vaccine)."). Likewise, the Wise et al. paper does not involve the HPV vaccine and is not specific to AA. *See* Pet'r's Ex. 79. Petitioner filed some case reports linking other vaccines to AA, but these do not indicate a relationship between the HPV vaccine and AA. These include papers linking the COVID-19 vaccine to AA, but Dr. Matloubian persuasively explained that "the COVID mRNA vaccine is not the same as the HPV vaccine which is made of only proteins." Tr. 116:13–19. After reviewing all of the medical literature Petitioner submitted, I find that he has not presented preponderant evidence of a relationship between the HPV vaccine he received and AA.

While Petitioner has not presented preponderant evidence relating the HPV vaccine and AA, he could possibly show a potential for cross-reaction by linking HPV infection, especially infection from the strains included in the Gardasil vaccine he received, with AA in a manner consistent with Petitioner's mechanism of molecular mimicry. Dr. Matloubian cited the Schattner paper, which proposes the requirement that "virus infections should be linked to autoimmunity[]" to demonstrate that vaccines can be implicated. *See* Resp't's Ex. A, Tab 13 at 6. This signals Respondent's contemplation that showing a link between HPV infection and AA may help Petitioner establish a connection between the two, but Petitioner has not shown preponderant evidence of such a link here.

Petitioner filed the Tu et al. paper to show that in "at least one study, [HPV] infection has been linked to the development of alopecia[] . . . ." Tr. 45:20–25. However, this paper does not provide preponderant support for the proposition that HPV infection could cause AA via molecular mimicry. Tu et al. reviewed patient medical records spanning a period of approximately twelve years, and they did not indicate when the patients in the HPV group developed AA relative to the onset of their HPV symptoms or the date they were infected with HPV. *See* Pet'r's Ex. 102 at 4. Furthermore, as Tu et al. only included patients who were symptomatic and received treatment related to their HPV in the HPV group, it is unlikely that patients in the HPV group were recently infected with HPV. This is because, as Dr. Matloubian explained, HPV infections can take years to cause symptoms or warrant treatment. *See* Tr. 133:24–135:7. Thus, the Tu et al. study does not support that HPV infection caused AA via Petitioner's mechanism or a similar mechanism, which Dr. Gershwin indicated would occur within weeks of antigen exposure. In fact, Tu et al. did not propose molecular mimicry as the possible mechanism at play in their study. They also acknowledged that "epidemiologic evaluation of HPV infection was challenging, as many

infections were not clinically recognized[,]" underscoring the point that patients with HPV infections or newly-acquired HPV infections may have been excluded from the HPV group. *See* Pet'r's Ex. 102 at 7. Furthermore, the Tu et al. paper does not indicate how many patients in their study were infected with the HPV strains contained in the Gardasil vaccine. Thus, it is unclear whether the authors would have found an association between HPV infection and AA if their study were limited to the HPV strains contained in the vaccine. Tu et al. also acknowledged that their "findings may not be applicable to non-Asian ethnic groups[,]" thus implying that their findings do not necessarily support a general association between HPV and AA. *See id.* at 8.

Petitioner filed additional articles, primarily centering on COVID-19 infection, in an attempt to show that AA is associated with infection. However, these papers are mostly case reports on a small number of cases. Nguyen and Tosti identified 143 patients who experienced flares of AA following COVID-19 infection, but all but seven of those patients had preexisting AA. Pet'r's Ex. 105 at 1. Petitioner has also failed to provide preponderant evidence that AA allegedly following COVID-19 infection is relevant to this case. Dr. Matloubian explained that coronaviruses, like COVID-19, are "very different from human papillomavirus[]" in that coronaviruses have an RNA-based genome and a membrane while human papillomaviruses have no membrane and a different type of genome. Tr. 114:20–115:5. Petitioner has not responded to this contention or explained how COVID-19 infection may be analogous to HPV infection. Birkett et al. stated that "AA can be triggered by viral infections such as influenza, [CMV], and the Epstein-Barr virus[,] Pet'r's Ex. 107 at 1, but Petitioner's own expert, after reviewing and submitting many articles in support of Petitioner's case, acknowledged that acute infections are not an established cause of AA. Tr. 62:12–14. He further acknowledged that he did not provide medical literature showing a CD8 response to any virus that has been associated with AA. Tr. 81:1–5.

To support his mechanism of molecular mimicry between components of the HPV vaccine and self-structures involved in AA, Dr. Gershwin indicated that the implication of cytotoxic T cells in AA suggests that an antigen is also involved. *See* Tr. 182:11–14. Dr. Matloubian acknowledged that cytotoxic T cells have been implicated in AA, but he denied that AA requires the introduction of a foreign antigen. *See* Resp't's Ex. C at 4; Tr. 107:7–18. He noted that potential triggers, such as stress and microbiome changes, do not involve the introduction of a foreign antigen. Resp't's Ex. A at 3. He also cited the Sundberg et al. mice study filed by Petitioner as an example of an AA-like disease appearing spontaneously, without an infectious source, and appearing to be genetics-driven. *Id.* In response, Dr. Gershwin acknowledged that stress is a potential trigger that does not involve an antigen, but he asserted that cases of AA associated with these triggers are typically "more patchy[]" and not "lifelong." Tr. 61:23–62:3. However, he also stated that he did not know of a way to determine whether someone would develop AA, which may be more patchy, or AA totalis. Tr. 88:21–89:2. Regarding the Sundberg et al. study, Dr. Gershwin asserted that "[t]here[is] something in these mice that[is] causing them to develop[] . . . CD8 T cells[]" and that the fact that the researchers did not find an antigen does not mean one was not present. Tr. 181:22–182:2–3. However, Dr. Gershwin's assertion is curious given that Sundberg et al. looked but did not find an infection present in the mice. *See* Pet'r's Ex. 66 at 8. Dr. Gershwin was "unaware of a clinical situation where [there are] organelle-specific cytotoxic T cells in the absence of an antigen." Tr. 182:11–14. However, Dr. Matloubian explained that "[t]here is no clear scientific evidence or consensus among researchers that [the cytotoxic T cells implicated in AA]

become activated through molecular mimicry with a foreign antigen." Resp't's Ex. C at 4. He cited other potential mechanisms associated with "loss of T cell or B cell tolerance[,]" including "escape of autoreactive T cells from the thymus[]" and a genetic defect. Tr. 107:7–18. I find Dr. Matloubian's explanation more persuasive than Dr. Gershwin's because, while it is undisputed that cytotoxic T cells have been implicated in AA, the literature filed in this case does not indicate that researchers necessarily or consistently associate these T cells with foreign antigens. Specifically, the Sundberg et al. study indicates the presence of T cells in mice with AA without an infection present. Thus, Petitioner has not established by preponderant evidence that a foreign antigen, such as HPV or the components of the HPV vaccine, are required to induce the cytotoxic T cells associated with AA.

Ultimately when discussing whether a foreign antigen is necessary to induce cytotoxic T cells, Dr. Gershwin emphasized that "[w]hat[is] critical is there[is] a CD8 T cell response." Tr. 184:1–3. Petitioner has not provided preponderant evidence that his proposed theory can occur because he has not shown that the HPV vaccine can induce the "critical . . . CD8 T cell response." Even if Petitioner were able to provide preponderant evidence for the first component of his theory, he still has not shown preponderant evidence of the second. He has failed to provide preponderant evidence that the HPV vaccine or HPV infection can cross-react with components of the Gardasil vaccine. Thus, Petitioner has failed to satisfy Prong One by a preponderant standard.

B. *Althen* Prong Two

Under the second prong of *Althen*, a petitioner must prove that the vaccine actually did cause the alleged injury in a particular case. *See Pafford*, 2004 WL 1717359, at *4; *Althen*, 418 F.3d at 1279. The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Hum. Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A petitioner does not meet this obligation by showing only a temporal association between the vaccination and the injury; instead, the petitioner "must explain *how* and *why* the injury occurred." *Pafford*, 2004 WL 1717359, at *4 (emphasis in original). The special master in *Pafford* noted petitioners "must prove [] both that her vaccinations were a substantial factor in causing the illness . . . and that the harm would not have occurred in the absence of the vaccination." 2004 WL 1717359, at *4 (citing *Shyface*, 165 F.3d at 1352). A reputable medical or scientific explanation must support this logical sequence of cause and effect. *Hodges v. Sec'y of Health & Hum. Servs.*, 9 F.3d 958, 961 (Fed Cir. 1993) (citation omitted). Nevertheless, "[r]equiring epidemiologic studies . . . or general acceptance in the scientific or medical communities . . . impermissibly raises a claimant's burden under the Vaccine Act and hinders the system created by Congress . . . ." *Capizzano*, 440 F.3d at 1325–26. "[C]lose calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280.

In Program cases, contemporaneous medical records and the opinions of treating physicians are favored. *Capizzano*, 440 F.3d at 1326 (citing *Althen*, 418 F.3d at 1280). Indeed, when reviewing the record, a special master must consider the opinions of treating physicians. *Capizzano*, 440 F.3d at 1326. This is because "treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" *Id.* In addition, "[m]edical records, in general, warrant

consideration as trustworthy evidence. The records contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions. With proper treatment hanging in the balance, accuracy has an extra premium. These records are also generally contemporaneous to the medical events." *Cucuras v. Sec'y of Health & Hum. Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). While a special master must consider these opinions and records, they are not "binding on the special master or court." 42 U.S.C. § 300aa-13(b)(1). Rather, when "evaluating the weight to be afforded to any such . . . [evidence], the special master . . . shall consider the entire record . . . ." *Id.*

Petitioner has not established a logical sequence of cause and effect between his vaccination and his AA. During his testimony, Dr. Gershwin testified that causation in this case is "deeper than just a temporal association[because there is also a] cellular and a mechanistic explanation for the temporal events . . . ." Tr. 50:18–23. Petitioner has failed to provide preponderant evidence of a "cellular and [ ] mechanistic explanation" in this case. Thus, in light of Dr. Gershwin's own statement, Petitioner's remaining argument for causation would be based solely on temporal proximity. It is well established in the Program that temporal proximity between a vaccination and injury is insufficient to support causation. *Moberly*, 592 F.3d at 1323 (quoting *Althen*, 418 F.3d at 1278) ("[N]either a mere showing of a proximate temporal relationship between vaccination and injury, nor a simplistic elimination of other potential causes of the injury suffices, without more, to meet the burden of showing actual causation."); *Sumner v. Sec'y of Health & Hum. Servs.*, No. 99-946V, 2015 WL 5173644, at *9 (Fed. Cl. Spec. Mstr. Aug. 13, 2015) ("[W]here a petitioner's expert views the temporal relationship as the 'key' indicator of causation, the claim must fail."). Dr. Gershwin supported causation by stating that Petitioner's HPV vaccination was "[t]he only immunological challenge" between Petitioner's HPV vaccination and alopecia onset. Pet'r's Ex. 7 at 4. However, Dr. Matloubian disagreed that this indicates causation and also explained that "very little is known about the environmental stimuli, if any[,] that may be required for development of [AA]." Resp't's Ex. A at 3. Dr. Matloubian explained a number of potential triggers besides the HPV vaccine that may have played a role in this case, including stress and Petitioner's use of an antibiotic in March of 2016. *See id.* at 4, 12. While petitioners can prevail on Prong Two without necessarily addressing alternative causes, the existence of possible alternative causes underlies why temporal proximity alone is insufficient.

Furthermore, Petitioner has failed to present preponderant evidence that he experienced an autoimmune reaction following his HPV vaccination. While this evidence is not mandatory, evidence of such a reaction could support Petitioner's contention that his vaccination caused autoimmunity, which then led to his injury. However, Dr. Gershwin acknowledged that there would be no way to distinguish between vaccine-caused and idiopathic alopecia. Tr. 84:23–85:5. He indicated that a difference could potentially be demonstrated through research efforts that have not been undertaken, but he conceded that he did not have evidence of an autoimmune reaction in this case. Tr. 84–85. Dr. Gershwin could not identify evidence of inflammation in Petitioner's alopecia, and he instead noted that such inflammation in an AA case would need to be observed "under a microscope." Tr. 93:2–15. Ultimately, Dr. Gershwin was unable to identify anything in Petitioner's medical history besides temporal proximity to connect his vaccination and injury. *See Cordova*, 2021 WL 3285367, at *18 (finding that the petitioner did not satisfy Prong Two because "only a temporal association links his AA onset to the first HPV dose . . . [and because t]here is

no evidence of any immediate reaction or measured autoimmune/inflammatory process that preceded onset[]"). Thus, Petitioner has failed to satisfy Prong Two by a preponderant standard.

C. *Althen* Prong Three

To satisfy the third *Althen* prong, a petitioner must establish a "proximate temporal relationship" between the vaccination and the alleged injury. *Althen*, 418 F.3d at 1281. This "requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan*, 539 F.3d at 1352. Typically, "a petitioner's failure to satisfy the proximate temporal relationship prong is due to the fact that onset was too late after the administration of a vaccine for the vaccine to be the cause." *Id.* However, "cases in which onset is too soon" also fail this prong; "in either case, the temporal relationship is not such that it is medically acceptable to conclude that the vaccination and the injury are causally linked." *Id.*; *see also Locane v. Sec'y of Health & Hum. Servs.*, 685 F.3d 1375, 1381 (Fed. Cir. 2012) ("[If] the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness.").

Although a temporal association alone is insufficient to establish causation, under the third prong of *Althen*, a petitioner must show that the timing of the injury fits with the causal theory. *See Althen*, 418 F.3d at 1278. The special master cannot infer causation from temporal proximity alone. *See Thibaudeau v. Sec'y of Health & Hum. Servs.*, 24 Cl. Ct. 400, 403–04 (1991); *see also Grant*, 956 F.2d at 1148 ("[T]he inoculation is not the cause of every event that occurs within the ten[-]day period . . . [w]ithout more, this proximate temporal relationship will not support a finding of causation." (quoting *Hasler v. United States*, 718 F.2d 202, 205 (6th Cir. 1983))).

Petitioner has presented preponderant evidence that his AA symptoms began approximately two weeks after his HPV vaccination. Dr. Gershwin stated that "onset within [fourteen] days" is "consistent with generation of a CD8 response." Pet'r's Ex. 7 at 4. Dr. Matloubian agreed that CD8 T cells can cause dysfunction within one to two weeks. Tr. 164:11–15. Therefore, Petitioner has provided preponderant evidence of a proximate temporal relationship pursuant to Prong Three. However, because Petitioner has not provided preponderant evidence that the HPV vaccine can induce cytotoxic T cells and thus cause AA through molecular mimicry or that it did so in this case, Petitioner has not established that he is entitled to compensation.

VI. Conclusion

After a careful review of the record, Petitioner has failed to prove by preponderant evidence that his AA was caused-in-fact by his May 16, 2016 HPV vaccination. Accordingly, I **DENY** Petitioner's claim and **DISMISS** his petition.[70]

IT IS SO ORDERED.

[70] Pursuant to Vaccine Rule 11(a), entry of judgment is expedited by the parties' joint filing of a notice renouncing the right to seek review.

s/Herbrina D. Sanders
Herbrina D. Sanders
Special Master